production technology. If it is small size, a series of channels will be placed on one base, and it also becomes possible to attain many separation simultaneously by it. However, an instrument should be made the size of sufficient like for both the inside of an instrument to be transported to hundreds of particles at least at the same time it moves independently mutually while the charged particle which should be separated dissociates. When a charged particle is an electrification molecule, the conditions of this latter are the minimum size in an instrument 50 to 500 of the size of a molecule It can fill easily by manufacturing in a twice as many size as this.

[0053]

Much material can be used about a base, channel walls (it can set to II type instrument), and an electrode. One restriction is the point that every material exposed to a separation lane must be inertness substantially to the contents of lanes, such as a medium to be used and a charged particle which should be separated. Originally material is inertness or it must be protected by passivation layers, for example, the oxidized silicon layer arranged at the electrode upper part. In order to make detection of the separated particles easy, it is preferred that a base is what enables use of fluorescent labeling. In this way, the base should be permeability substantially to the light of the fluorescence wavelength excited and induced. Amorphous oxidized silicon is one example of the base permitted to fluorescent dye of most by which normal use is carried out to a sign DNA fragment. The example of others of the material permitted is indicated to Section 5.5.

[0054]

The charged particle which should be separated can be made into the range to the complex of a molecule to the individual molecule of arbitrary numbers and a kind of all sizes, and the particles of macroscopic size.

[0055]

A separation lane is full of the separation medium in which it crawls preferably and the characteristic of shoes is shown. The 1st characteristic is dissolving and ionizing the particles which should be separated. The 2nd characteristic is that the mold of the charged particle which should be separated has a different dispersion ratio in the medium. It is so more desirable as a medium that the difference in a dispersion ratio is so large that a dispersion ratio is large as a whole. The 3rd characteristic for quick separation is that a medium bears high potential inclination. Therefore, in impression potential, a medium is preferred and it is so desirable that it is resistance and a decomposition electric field is high to electrolysis. It is preferred that media are finally a small dielectric constant and small ionic strength. It is because the intensity of an electric field decreases by dielectric shielding by a medium, and ion cover by content ion. Of course, the characteristic of this latter receives restriction by the necessity for the solvation of an electrification molecule. That is, it is because a counter ion exists, so a high dielectric solvent and the limited ionic strength are generally needed.

[0056]
An experiment can determine most easily the separation medium which suits these conditions about the charged particle of the specific mold which should be separated. In order to separate biopolymers, such as DNA, a suitable separation medium is the aqueous solvent or aqueous buffer ordinarily used in the usual electrophoresis. Or a denaturation solvent like a formamide may be sufficient as a medium. The solvation of the molecule can be carried out by a charge state, and it is possible [sufficient], for example, usable also in other organic solvents, such as DMSO (dimethyl sulfoxide) or an alcohol solution. Thin gel or a polymer solution is also a possible separation medium.
[0057]
An eliminator implement can be operated at every temperature which suits a component and the separation medium to be used. unless in particular all examples and calculations that are raised here are specified -- ambient air temperature -- about -- Operation at 298 degrees K is assumed. In order [which holds a separation medium uniformly between each separation lane irrespective of operating temperature] to carry out, it is important to make a heat gradient into the minimum. This is attained by installing so that heat contact of the upper part of an eliminator implement, a pars-basilaris-ossis-occipitalis base, or its both may be suitably carried out with a heat sink or a heat source.
[0058]
The following divisions explain further two examples called an I-beam and II type in which the eliminator implement shown in drawing 1 is specific. In an I-beam instrument, the channel which forms a separation lane like the channel 15 is etched into one field of the base 11 or 12. In II type instrument, a separation channel is formed by arranging channel walls parallel on [one] a base. Also in which example, an electrode is arranged at one side of a base.
[0059]
5.1.1. I-beam instrument drawing 2 is an exploded view of the typical example of an I-beam instrument. The instrument 10 contains the top base 11 and the pars-basilaris-ossis-occipitalis base 12. The one or more separation channels 15 are manufactured in the top base 11, for example by etching or micro machining. Separation takes place along with a channel, therefore the separating direction S is become final and conclusive by this channel. The width of the shape of one channel is abbreviation preferably. 50 micrometers and height. It is a rectangle from the yen half [about] which is 10 micrometers. The thing of smaller height and width is preferred. It is because a little samples are needed for analysis. The range to the big size like [it is equal to the width of the electrophoresis instrument on the basis of the gel from the former] may be sufficient as width. The sufficiently small thing of height is preferred so that it may be made to localize particles enough with the generated potential in an ON state. This ON state is most simply determined by the experiment about the shape of the given instrument

which uses the particles representing the particles which should be separated. Each channel is substantially extended to the overall length of a base, and this is typically. Although it is 1-10 cm, it is selected in accordance with the designing method of Section 5.3 and Section 5.4. It is made to approach as much as possible between channels, and it is made into a desirable distance almost comparable as the width. In the upper plate 11, the hole of the loading port 16 of drawing 1 can be manufactured so that it may indicate further below. The diameter of this inlet is chosen so that loading of the particles which should be separated can be carried out into a lane. Although parallel may be substantially sufficient as a channel, it may be completed from the large interval in the loading port neighborhood to the narrow interval in an observation zone. The channel manufactured to the upper plate is sealed and the closed particle separation lane is made to form by joining the base of two sheets. In order to carry out the external voltage supply 17 and electrical connection, a top base has a dent to a pars-basilaris-ossis-occipitalis base so that an electrode pad may be exposed.

[0060]

It meets mutually, and it is two two or more electrodes which geared mutually, and each of the group of two or more electrodes installs the electrode connected to one side of the two electrode pads 13 and 14 in the planate upper surface of the pars-basilaris-ossis-occipitalis base 12. Or an electrode can be installed in the field of the top base 11 which is not planate. The electrodes 20 and 22 are the examples of representation of two or more electrodes connected to the pad 13, and the electrodes 21 and 23 are the examples of representation of two or more electrodes connected to the pad 14. These electrodes are extended in the direction which intersects perpendicularly substantially to the separation axis S preferably. Although it is not so desirable, a thing leaning to the separation axis and the separation lane also has an electrode so that it may be generated in arrangement of the separation lane to converge. An effect becomes small and the separability of particles worsens, so that the angle of an inclination is large. The thickness of each of these electrodes is about 0.1-0.2 micrometer preferably. Although it is small and is not so desirable 1 micrometer It may be small. However, the thing of big size does not necessarily block operation of an instrument. Although the width of each of these electrodes shows the main size by R', it is preferably smaller than about one to 2 micrometer. Although R' of a larger value than this does not necessarily block operation of an instrument, a result which is not more preferred is brought on the scale of R'^2. Main sizes are abbreviation. 1 micrometer A thing can be easily attained with standard micro production technology. Preferably, each of two or more electrodes connected to the electrode pads 13 and 14 keeps the uniform distance L, and is arranged periodically. For example, it is separated from the electrodes 20 and 22 of the distance L, and their electrodes 21 and 23 are also the same. Preferably, it is arranged so that each of two or more electrodes may become the interval R mutually. For example, it is separated from the center of the electrodes 20 and 21 of

the distance R, and it is the same. [of the center of the electrodes 22 and 23] Preferably, R is almost equal to R', and on the other hand, L is selected so that R/L may become smaller than about 0.1. However, the thing of the ratio to 0.5 can also be used. How to select optimal R, L, and R/L is indicated to Section 6.2 about main size R' which can be attained in the selected production technology. Or since particle separation of a certain kind of aspect is optimized according to the model indicated to the 5.2nd and Section 5.3, R, L, or R/L can be regularly changed in accordance with a separation axis.

[0061]

Drawing 3 shows the sectional view in alignment with the axis 3-3 which intersects perpendicularly to the separating direction S of the instrument 10. The top base 11 and the pars-basilaris-ossis-occipitalis base 12 form three channels, such as the channel 15, and these are sealed and form the separation lane. If the typical electrode 20 is necessary, it was preferably covered with passivation layers and is extended along with the pars basilaris ossis occipitalis of a channel.

[0062]

Drawing 4 A shows two two or more electrodes more to details in graph. The electrodes 20 and 22 of one two or more electrodes are connected to the electrode pad 13, and the electrodes 21 and 23 of two or more electrodes of another side are connected to the pad 14. It is separated from the electrode in one two or more electrodes of the distance L. It is separated from the center of the electrode which adjoin ** between electrodes of the distance R. The width of each electrode is R'. Therefore, the distance between the ends which the electrodes 21 and 22 adjoin is L-2 R-R', and the distance between the ends which the electrodes 20 and 21 (or 22 and 23) adjoin is R-R'. The pads 13 and 14 are potential, respectively. - Electrification is carried out to $V_0/2$, and $+V_0/2$. In the case of $V_0>0$, the separating direction of a positive charged particle is S. In the case of $V_0<0$, S is a separating direction of a negative charged particle.

[0063]

Drawing 4 B is illustrating ideally the profile of the potential generated by two two or more electrodes observed in accordance with the separation lane. The minimum near [where potential was connected to the pad 13] the electrode - A series of potential wells which change to maximum $+V_0/2$ near the electrode connected to the pad 14 from $V_0/2$ are formed. This potential is generally a serration form, and is spatially periodic, and each cycle of a potential well has the minimum located uniformly and eccentrically. Each cycle has the portion 32 between the position 36 separated in the distance R, and 37 which goes up more rapidly [it is comparatively short and], and a portion between the position R35 separated by distance L-, and 36 which descends more nearly gently [it is comparatively long and]. A separating

direction and the arrow S are the directions of [from one minimum point] the nearest adjoining maximum points. That is, the arrow S is the direction of [from the minimum point 36] the nearest adjoining maximum points 37. The potential well is uniform about all the wells in these directions, and all are located in a line the same direction and here, without the arrow S. It is clear that this potential well's it is in the immovable state also in the space near the electrode formation part. When electrification of the pad is carried out to opposite potential, a rise and a downward portion take the place.

[0064]

The minimum size about each potential well generally receives restriction by the desirable aspect which contains the particles which should be separated hundreds or more. A well must be so large that the particles to contain can move independently that there is no correlation in any way. In the desirable example of application from which an electrification biopolymer is separated, R is abbreviation. This will be filled if larger than 0.1 micrometer.

[0065]

Drawing 5 shows the sectional view of the instrument 10 in alignment with the axis 4-4 of drawing 2 which is a separating direction in separation lanes, such as the lane 15. A separation lane is the upper part in the top base 11, and a lower boundary is divided with the pars-basilaris-ossis-occipitalis base 12, these bases have the distance of H, and this has height of a lane. The height of a lane is 10 micrometers preferably. Bigger height is also possible although are selected, and there is restriction that it is strong to potential making particles localize by an ON state enough. It intersects perpendicularly substantially to the separating direction S, it exposes to a separation lane, and the electrode which is generally in 20, 21, 22, and 23 on the bottom plate 12 generates potential. height d with them -- although it is width [of one to 2 micrometer] R' preferably and the interval R is about 2R' preferably, since separation with the quicker smaller interval can be performed, it is more desirable. [these preferred electrodes and] [smaller than about 0.1 - 0.2 micrometer] As for an electrode, it is preferred to be periodically arranged in the fixed distance L selected so that R/L might become 0.1 or less preferably. Or it is R/L although it is not so desirable 0.3 It carries out the following. Although an effect is inferior, an instrument continues functioning also by the marginal ratio 0.5 (namely, symmetrical well).

[0066]

In order to make loading of the particles before separation easy, it is advantageous to an instrument to install a loading part. In order to make it easy to carry out loading with the present loading art, a loading part has a diameter of about 50 - 100 micrometers which is the size of a micropipette preferably. Therefore, this serves as a convenient measure for the width and the interval of a separation lane. Or since the loading port of desirable size is made possible, it can be made to converge so that it may be made a narrower separation lane, and

can be made to take a large interval by a loading part and an interval may be narrowed in an observation zone. In order to attain the optimal separability and speed, all the particles are drawn into one potential well before separation, and the interval between a series of potential wells has [making it be the above] a preferred thing.

[0067]

Drawing 6 which is expansion and the exploded view of the instrument 10 about the loading port 16 of drawing 1 shows the loading part fitted so that these characteristics might be filled. The particles which should be separated are introduced into the part 52 inside the separation lane 15 by the pipette 51 or the same mechanism in the part 51 from the exterior of an instrument. The electrodes 54 and 55 under the loading port 16 have made it take the big interval to the grade of the diameter of the loading port 16. Sufficient time to draw [of the electrode 55] to the neighborhood and the part 53 very much and potential are given to an electrode pad, therefore the electrodes 54 and 55 for all the particles during loading of particles, or after loading. The same method as the determination of t_{on} indicated to Section 5.3 can estimate sufficient time. Separation of particles can be started after drawing and carrying out the trap of the particles. Since initial distribution of the particles which should be separated is made smaller, another electrode disposition can also be used for a loading field. For example, since all the particles between the electrodes 56 and 55 are made to localize before a separation start, the electrode 56 can also be made into potential with a spasm strong another more in the electrode 55.

[0068]

5.1.2. II type instrument drawing 7 is an exploded view of the typical mode of II type instrument which is a desirable mode of an eliminator implement. The instrument 10 contains the top base 11 and the pars-basilaris-ossis-occipitalis base 12. The same electrode pattern as an I-beam instrument and the electrode pad to connect are arranged at the plate-like upper surface of the pars-basilaris-ossis-occipitalis base 12. Or an electrode can be installed in the non-plane surface part after channel walls were manufactured, or the undersurface of the top base 11.

[0069]

Only one difference in the instrument of two molds is that a separation lane is formed by manufacturing straight channel walls substantially along the separating direction S in II type instrument to one side of two bases. Drawing 7 is the upper surface of a pars-basilaris-ossis-occipitalis base, and shows the channel walls 41 and 42 which form the separation lane 15 manufactured on the electrode pattern manufactured beforehand. The separation lane is exposed to an electrode like an I-beam instrument. Although the separating direction S and this electrode cross at right angles substantially preferably or is not so preferred, it has an angle of inclination below 48 degrees. The shape of a separation lane is the same substantial rectangle as the rain size of an I-beam instrument.

[0070]
The upper part and a pars-basilaris-ossis-occipitalis base are joined so that channel walls may form the separation lane sealed with the upper part and a pars-basilaris-ossis-occipitalis base. In order to carry out electrical connection to the voltage source 17, the inconsistency part to a pars-basilaris-ossis-occipitalis base is given to a top base so that a pad may be exposed.
[0071]
Drawing 8 shows the sectional view of the instrument 10 in alignment with the axis 8-8 of drawing 7 which intersects perpendicularly with the separating direction S. The top base 11 and the pars-basilaris-ossis-occipitalis base 12 serve as a boundary of three channels. The boundary is made with the walls 41 and 42 in which the channel 15 was manufactured by the one surface of a base. The typical electrode 20 is extended along with the pars basilaris ossis occipitalis of a channel.
[0072]
5.2. The method of this invention incorporated into the device explained in the operation outline of Section 5.1 of the method is shown in drawing 9 A-E. These figures are shown according to separation of the charged particle of two types, i.e., the larger rod as 91, and it depends for them, and they are indicated to be large particle types with the smaller rod as 92, and it depends for them, and they show separation with a small particle type. Potential is shown by the curve 90. In drawing 9 A, and 9C and 9E, a serration form is assumed to time t_{on} and a flat form is assumed to time t_{off} at drawing 9 B and 9D. When these particles are single stranded DNA molecules of various sizes, a possibility that a molecule will take the shape of a ball becomes high actually.
[0073]
Drawing 9 A shows the start of separation and the trap of all the particles is carried out to the potential well of most left-hand side at this time. The potential to t_{off} is a flat form and particles are uniformly spread in both directions along with a separation channel in drawing 9 B at this time. Diffusion is shown by the schematic illustration as 93. In drawing 9 C, the trap of the particles which it was assumed that potential was a serration form again, carried out the drift to the right, and only the distance R followed in the direction of the following potential well at least is attracted and carried out to a middle well. However, the trap of the particles whose diffusion length is less than R is attracted and carried out to the potential well of the basis of most left-hand side. Small particles have a possibility higher than having a smaller diffusing constant of being spread to a distance than large particles, and although it is two with a small grain, it is one by large particles to reach a middle potential well, rather than having a larger diffusing constant. In drawing 9 D, potential is a flat form again and it is uniformly spread in both directions from the potential well of both 93 and 94. Finally, in drawing 9 E, it is assumed that

potential is a serration form again, it is fully spread from the potential well of middle [one] of the small particles to a distance, is induced the well of most right-hand side, a trap is carried out, and two small particles exist in a middle potential well. On the other hand, since large particles are not fully diffused to a distance, it does not exist in the well of most right-hand side, but only one large particle exists in a middle well. Therefore, it turns out that the particles which have a larger diffusing constant are selectively transported to right-hand side via a device.

[0074]

The difference in the forward motion of particles is based on diffusion of particles. A potential well is in constant ****** spatially, and only the work which induces particles minimum potential is presented at the time of impression. To significant diffusion when potential is not impressed, in particles, the distance R maintains a stationary state in a device, when [remarkable] large.

[0075]

Since it is expected that the diffusing constant D of DNA will be dependent on the size of a molecule especially, Therefore, since being dependent on severalN of the base in the fragment of a single strand or a double strand is expected, A DNA molecule is separable by this method (Doi et al., 1986, The Theory of Polymer Dynamics, Clarendon Press, Oxford, p.300). The actual measurement of dsDNA and the theoretical predicted value to ssDNA are given as follows as a value to solution. : [Equation 1]

$$D_{dsDNA} \approx 1.14 \times 10^{-6} N^{-1} cm^2/s$$
$$D_{ssDNA} \approx 1.14 \times 10^{-6} N^{-0.59} cm^2/s \qquad (1)$$

For example, refer to Weast, ed., 1987, Handbook of Chemistry and Physics, Chemical Rubber Publishing Co., Boca Raton,FL and Section 5.4.

[0076]

Next, some are described about an operating condition over a device. Separation becomes quick, so that, as for a separation rate of potential, eccentricity of electrode becomes large depending on eccentricity of electrode of potential. Eccentricity of electrode means the minimum position of potential to a potential well, and eccentricity of electrode of potential becomes large, so that the minimum of potential approaches the maximum contiguity maximum. For example, in a series of serration form potential which has the same synchronization L, it operates most quickly at the time of potential which has the smallest R/L ratio. Of course, R cannot be substantially made smaller than structure size R' obtained with specific production technology, and cannot be made so small that a potential gradient obtained exceeds a destructive electric field of a separation medium, either. It is preferred to enlarge L enough so that a potential well can carry out the trap of at least hundreds of independent move particles.

[0077]
It is required to enlarge voltage V impressed by crossing an electrode pad enough so that it may become [whether t_{on} is made within suitable limits compared with t_{off}, and] small preferably. However, don't make it so large that substantial electrolysis takes place in an electrode, a destructive electric field of a separation medium is exceeded or resolution of separation is barred by resistance heating of a separation medium.
[0078]
Section 5.3 is shown R, L and R/L based on a model of a separation method in a narrow channel substantially provided with a lateral electrode, t_{on}, t_{off}, and a selection method of V. With this model, an operation parameter to a actual device must be correctly predicted within the limits of predetermined. When required, optimization processing by the usual experiment can also determine an exact operation parameter. For example, when separating a DNA molecule, an operation parameter predicted can be optimized by operating a device using a DNA standard including a ladder mold structure object of a fragment which has known length.
[0079]
A method of this invention is applicable to a charged particle of all sizes. A charged particle used as a candidate for separation attains to a complex of each molecule to a molecule of arbitrary numbers and a kind of all sizes, and particles of a macroscopic size.
[0080]
5.3. a detailed foreword of operation of a method -- this section explains operation of a method of this invention in detail. :L which uses the following variables in this explanation Space cycle of potential.
[0081]
Distance from the minimum of R potential to the maximum contiguity maximum.
[0082]
(It is the measure of eccentricity of electrode of each cycle of potential how smaller [than L/2] R is)
P A time cycle of potential ($P=t_{on}+t_{off}$).
[0083]
f Time frequency of potential ($f=1/P$).
[0084]
Time when t_{on} potential is impressed. Particles are POTENSHI in the meantime. A trap is induced and carried out to YARUWERU.
[0085]
Time when t_{off} potential is not impressed. Particles are freely in the meantime. It can be spread.

[0086]
Q An electric charge of a charged particle.
[0087]
V_0 impression potential difference.
[0088]
T Temperature.
[0089]
A diffusing constant of a charged particle of one type used as a candidate for D separation.
[0090]
D+delta D Diffusing constant of a charged particle of another type used as a candidate for separation (deltaD means a difference of a diffusing constant).
[0091]
The number of time cycles of potential to N_{cyc} complete isolation processing.
[0092]
Total time of T_{tot} complete isolation processing ($T_{tot}=P*N_{cyc}$ and $N_{cyc}=f*T_{tot}$).
[0093]
Drift velocity of a charged particle in inside of V_{drift} potential.
[0094]
An overall length of L_{tot} separation lane.
[0095]
A desirable embodiment over a method and a device of this invention is shown [1st]. A method of 2nd choosing an operation parameter and a device parameter most appropriately is shown. Other model operating modes of this invention within the limits are explained [3rd].
[0096]
5.3.1. an embodiment of this invention -- explanation which is seen from time change potential and judging standards over a parameter of an operating method of a method of this invention, and these judging standards, and is attached without a model of desirable this invention is included in this section. [spatial and] It assumes first that it is deltaD<<D, and a case of deltaD>=D is explained continuously.
[0097]
The electrogram 10 generally shows potential V(x) usable with this invention with a schematic illustration as a function of the distance x in alignment with a separation axis. This potential is spatially repeated with the space cycle L. In addition, potential without a space cycle can also be used by this invention. An eccentricity is given to each cycle of potential and it must be made for the minimum of potential to have to approach more the maximum which adjoined in the one direction in alignment with a separation lane. This direction is the separating direction

S of particles. An interval of the minimum and the maximum contiguity maximum is expressed with R, and are R<L/2. For example, although it is separated from a minimum of 1003 of the distance R L / below a maximum of 1002 to 2, only distance L-R exceeding L/2 is separated from a maximum of 1001 of contiguity. [of contiguity] All the minimum is close by the maximum which adjoined in the direction of S. This potential is almost equal to potential generated near the electrode pattern of the device types I and II.

[0098]

In the case of V_0>0, potential of drawing 11 A-D separates just electrified particles in the direction of S. In this case, although transported to a counter direction via a device, it is not necessary to necessarily separate particles electrified in negative. The polarity of potential must be reversed in order to separate particles electrified in negative in the direction of S. That is, it must be referred to as V_0<0. In the case of the latter, although transported to a counter direction via a device, it is not necessary to necessarily separate just electrified particles. Both charged particles are continuously separable by carrying out loading of the particles to a loading zone of one end of a device, operating a device to an advantageous thing with one polarity first, and operating it with polarity reverse next. However, in a desirable embodiment specific to separation of DNA, all the particles are considered to have negative charge.

[0099]

Spacial configuration V(x) with precise potential is not important for carrying out this invention in a top. An important thing is that potential has the maximum of potential and the minimum of potential which appear by turns in accordance with an axis of separation. A well makes only the distance L estrange mostly. Next, all the maximum and all the minimum must be eccentrically arranged so that each minimum may approach more the maximum which adjoined towards separation from the maximum which adjoined in the direction opposite to the direction of separation. The minimum and maximum contiguity maximum distance is about R. It is decided for convenience by the distance L and R that a field of such potential is characterized. A method of this invention can be applied to arbitrary potential with which it is satisfied of these constraints, and particles are divided into a separating direction of an electric charge induced a well. It is preferred that potential has a periodic similar potential well, and it assumes spatial period nature altogether in the following explanation. However, spatial period nature is not necessarily required for this invention.

[0100]

In order to acquire the greatest separation efficiency (i.e., in order to consider it as the minimum separation time), it is preferred that potential is uniform in a direction which crosses a moving shaft. However, when an electric field vector has an ingredient vertical to an axis of separation, it puts in another way and it has an ingredient vertical to displacement which met towards separation, a method of this invention and a utilization ratio of a device fall. Operation

efficiency of this invention is cos (theta) approximately. However, theta is an angle of an electric field vector to displacement along a separating direction. Therefore, it turns out that this invention functions to almost all relative directions between an electric field and a separating direction. However, it is preferred that all the electric field vectors meet an axis of separation substantially. In this case, meeting substantially means that theta is less than about 45-50 degrees, i.e., cos (theta) is larger than about 0.5.

[0101]

In a specific embodiment of this invention, it is possible to adjust an operation parameter so that influence of the heterogeneity of a transverse direction of potential may be suppressed to the minimum. For example, in [potential is generated by an electrode which adjoined a separation lane and] the device types I and II for example potential, Electrode size and an interval when an embodiment over time t_{on} over time t_{off} which changes to an ON state substantially compares with desirable separation rain width from an OFF state substantially may become uneven in a transverse direction of a moving shaft owing to. Since potential decreases as it separates from an electrode, a potential well becomes the deepest in a place nearest to an electrode. When rain width is larger than the minimum electrode spacing, and when an electrode does not surround a channel thoroughly, a potential well may become weak on the side of the furthest lane from an electrode. However, this does not become a problem in this invention. It is because t_{on} is chosen the optimal so that a charged particle may be induced an electrode and a trap may be carried out [1st], and t_{off} is chosen the optimal so that particles may diffuse a distance almost equal to an electrode spacing at the longest further. Therefore, since particles separated stagnate in a field of a comparatively deep potential well during the optimal operation of a device, unevenness of potential on an electrode can be disregarded substantially. Potential near the separation rain wall may be confused. Also in this case, since a charged particle stagnates in a comparatively deep place of a potential well, unevenness can be disregarded substantially.

[0102]

Also in time, potential changes again. In this case, a required thing is only changing potential to the 2nd strength that particles diffuse in both directions comparatively freely, although probability of diffusion to the maximum contiguity potential well from the 1st strength by which the trap of the particles is attracted and carried out to a spatial potential well is not zero. this probability -- 0.1% or less of very small value -- or it may be about 100% of very large value. It is preferred to optimize so that the quickest possible separation can be performed. Although a temporal response is periodic, it has the cycle P and the frequency f and it assumes that it changes between an ON state and an OFF state by the following explanation only for expedient convenience, it is not limited to this. Potential**$V_0/2$ are impressed to time t_{on}, and

potential is not impressed in time t_{off}. Therefore, potential is an OFF state in time t_{on} among each cycle of an operation of the time T at ON state and time t_{off}. However, they are $t_{on}+t_{off}=T$ and f=1/T.

[0103]

Although a method of this invention has ** modeled using potential of two periodic states in time, it can also use potential which has other change for this invention. A temporal response does not need to be [1st] periodic. For example, a time cycle may be systematically changed as separation progresses. Other states may be included in a cycle the 2nd. For example, a state for centralizing particles on a bottom of a well more strongly at the time of a start of each cycle may be included so that the parameter R may become a smaller value. Potential may be continuously changed with time.

[0104]

When desirable constraints potential of a method parameter is an ON state, a potential well must be [that the trap of the charged particle separated should be attracted and carried out against thermal agitation] deep enough. This condition is satisfied, when V_0 is large enough and the following inequalities are materialized.

[0105]

[Equation 2]

$$\frac{V_o Q}{k_b T} \gg 1 \qquad (2)$$

(k_b is a Boltzmann constant)

When potential is an OFF state, the particles of the diffusing constant D in the well whose number is one must have probability $alpha_D$ which diffuses only the distance R towards separation toward the following potential well. This probability is advantageously decided by optimizing t_{off} so that separation may be performed [whether it can do and] promptly. In the desirable model for this invention, this condition is a following formula. : [Equation 3]

$$\alpha_D = 1/2 erfc\left(\frac{R}{\sqrt{4Dt_{off}}}\right) \qquad (3)$$

It is expressed as a relation of R and t_{off} which are given as be alike. However, "erfc" is a supplement error function.

[0106]

When potential is an OFF state, particles of the diffusing constant D should have the probability that will diffuse only distance L-R and it will return toward a front potential well, but this probability is $alpha_D$ / less than [100] preferably. In a desirable model for this invention, such a result is obtained, when R, L, and $alpha_D$ satisfy the following conditions.

[0107]

[Equation 4]

$$\sqrt{4Dt_{off}} \leq R \ll L \qquad (4)$$

The probability which reaches to the potential well where particles diffuse only distance L+R, and which has them ahead of the following maximum contiguity well is more nearly inevitably [than the probability that will diffuse only distance L-R and it will return] small.

[0108]

These conditions are satisfied easily. For example, in the case of $alpha_D$=0.05 and R/L=0.1, the probability diffused to an opposite direction is about 10 extremely small $^{-50}$, and the probability diffused exceeding one potential well is still smaller.

[0109]

When choosing a design parameter for an operation parameter for a method of desirable model this invention, and a device of this invention, it is possible to constitute various models. For example, an exact motion of a charged particle in a separation medium with exact potential generated by an electrode actually used which is spatial and is exposed to a time structure and such potential can be determined by solving a known differential equation of electromagnetism and particle motion. An equation of these by a standard method. It can solve numerically (Press et al., 1992, Numerical Recipes in C, 2nd ed., Cambridge Univ. Press, and New York (explanatory of a numerical solution)). It is also preferred to build an approximation model which instead gives a suitable result, or to optimize a parameter based on an experiment using a actual device. case where an exact model is used according to this desirable method a short time -- and, by low cost, suitable accuracy to an operation parameter and a design parameter is obtained.

[0110]

A desirable approximation model describes a method and a device of this invention as a random walk which has a drift. For example, refer to Wax, ed, 1954, Selected Papers on Noise and Stochastic Processes, Dover Publishers, and New York. A random walk ingredient is produced by diffusion of particles in case potential is an OFF state, and a drift component is produced by carrying out the trap of the particles to the minimum of potential, when potential is

an ON state. A desirable model is explained in this specification, referring to desirable potential of almost a serration form characterized with the distance L and R, and particles by which the trap was carried out in early stages to one potential well in a loading zone. In this case, a drift to the direction of separation in each cycle of potential is $alpha_D L$. However, $alpha_D$ is the probability of particles of the diffusing constant D diffusing only the distance R, and entering into the maximum contiguity well. Under desirable parameter restriction conditions, probability which particles retreat or move forward and diffuse exceeding one potential well can be disregarded. A variance of a particle position for every potential cycle increases according to $L (alpha_D - alpha^2_D)^2$. A concentration profile of particles observed by central limit theorem over a potential well of ** and many becomes Gaussian distribution. For example, refer to Wax, ed, 1954, Selected Papers on Noise and StochasticProcesses, Dover Publishers, and New York.

[0111]

Therefore, after passing through the time t, Gaussian distribution of particle concentration after tf cycle has a peak called $<x_D (t)>$, and this peak is a following formula. : [Equation 5]

$$\langle x_D(t)\rangle = tf\alpha_D L \qquad (5)$$

It is come out and given. It is called $deltax_D$ (t) and the half breadth of the Gaussian distribution of particle concentration is a following formula. : [Equation 6]

$$\left[\langle \delta x_D^2(t)\rangle\right]^{1/2} = \left[\langle x_D(t) L(1-\alpha_D)\right]^{1/2} \qquad (6)$$

It is come out and given. Characterization of the particle concentration which crosses some potential wells is made by these formulas.

[0112]

Since particles are freely spread when potential is an OFF state, $alpha_D$ is calculable as a portion of the particles which diffuse only the distance R at least rightward between time t_{off}. According to the theory of standard diffusion, this is a following formula. : [Equation 7]

$$\alpha_D = \frac{1}{2}\mathrm{erfc}\left(R/\sqrt{4Dt_{off}}\right) \qquad (7)$$

It is come out and given. For example, refer to Wax, ed, 1954, Selected Papers on Noise and Stochastic Processes, Dover Publishers, and New York. In this formula, a supplement error

function is a following formula. : [Equation 8]

$$\mathrm{erfc}(x) = (2/\sqrt{\pi}) \int_x^{\infty} dt \exp(-t^2). \qquad (8)$$

It comes out and defines. About the polynomial approximation to erfc(x), Abramowitz et al., 1972, Handbook of Mathematical Functions, Dover Publishers, and New York have a statement. In the formula 7 to alpha_D, it is assumed that the initial distribution of the particles in each potential well has dramatically narrow width. The width of the initial density distribution of the particles by which a trap is actually carried out to the bottom of each well when potential has limited width is a width grade of an electrode. However, this difference only affects numerical description of alpha_D. In particular this does not affect the model of the formulas 5 and 6. It is because it is necessary to understand each functionally how alpha_D is dependent on the diffusibility D in these cases.

[0113]

This model shows how a particle kind of different diffusibility is separated by this invention like. It is shown that 1st the formulas 5 and 7 are transported towards separation more quickly than a kind with diffusibility with a smaller kind with bigger diffusibility. separation of a kind of diffusibility in which the formulas 5 differ again -- the time t -- or going on linearly with cycle several N_{cyc} in a similar manner is shown. The formula 6 shows [2nd] that width of each kind of concentration profile increases with $t^{1/2}$. After sufficient cycle of potential of a number, since separation of a concentration profile to each kind advances more quickly than width of a concentration profile of arbitrary kinds, a concentration peak relevant to a kind of different diffusibility is spatially separated to such an extent that it can observe.

[0114]

The formula 7 shows how time required for separation is dependent on structure size of a device. Shape of a concentration profile of a seed and speed of separation of a seed are thoroughly decided by probability parameter alpha_D. Since this parameter depends only on a variable of a supplement error function again, the change of the structure size R can maintain balance by change of time t_{off}, and this variable is maintained as it is eternal. In order that R may involve linearly and t_{off} may involve in a form of a square root, if the structure size R decreases to one half, time required for separation will decrease to one fourth. The length of the whole device increases linearly with R (setting to fixed R/L). Therefore, in device length small enough, separation is performed more nearly promptly. In this case, if structure size is decreased using progress of ultra-fine processing technology, performance of a device can be raised directly. The device must be the minimum described previously, i.e., a size exceeding a

value with a larger digit number than size of particles separated.

[0115]

Drawing 11 A-D and drawing 12 A-E show an operation state of this invention where this model was followed. Drawing 11 A-D shows a detailed concentration profile of two sorts of particles A and B of different diffusibility in two adjoining potential wells shown with a schematic illustration as 1101 and 1102. However, the kind B has larger diffusibility than the kind A. The position 1108 written also as R is the maximum contiguity potential maximum which adjoined a minimum of 1101. In drawing 11 A, the potential 1107 is in an ON state, particles are induced the initial potential well 1101 and the trap is strongly carried out against thermal diffusion by the formula 2. The concentration profiles 1103 and 1104 of the kind A and the kind B are gauss types mostly in each well. In drawing 11 B, potential is switched to an OFF state and a molecule diffuses inside of a separation medium in both directions at speed according to the diffusibility of a molecule. At this time, the kinds A and B have the wider gauss type concentration profiles 1103 and 1104. However, since diffusibility is [the kind B] larger, a direction of the profile 1104 of the kind B is wide. Some kinds A of the profile 1103 and more portions of the kind B of the profile 1104 are diffused exceeding adjoining a maximum of 1108. In drawing 11 C, potential is again switched to an ON state, particles are again induced the wells 1101 and 1102, and a trap is carried out strongly. However, at this time, the trap of the particles diffused exceeding a maximum of 1108 is carried out to the well 1102, and the kind A and the kind B show the concentration profiles 1105 and 1106. The drift of these particles is ahead carried out exceeding one well. In drawing 11 D, potential is again switched to an OFF state and both kinds diffuse it towards the outside from both wells. Based on the symmetry of potential, a concentration profile of a molecule moved rightward selectively so that a kind of larger diffusibility might be transported more quickly.

[0116]

Drawing 12 A-E shows an operation state of a model of this invention in a scale containing many potential wells. a random walk for which these figures used a drift model -- ******** -- it creates from exact calculation. A horizontal axis meets towards separation and contains 30 potential wells. A vertical axis expresses concentration of the two charged particle kinds A and B separated. The kind A with lower diffusibility is expressed by the bar 1201, and the kind B with higher diffusibility is expressed by the bar 1202. Time t_{on} and t_{off} are chosen the optimal in accordance with a method of a statement. Drawing 12 A shows an initial state by which the trap of both kinds is carried out only to the 1st potential well. Drawing 12 B, and 12C, 12D and 12E show a concentration profile of a kind of both after 25 cycles, 50 cycles, 75 cycles, and 100 cycles, respectively. If the number of cycles increases according to a central limit theorem, it will come to carry out the Gaussian distribution of these profiles over many potential wells. It is clear that the kind B is transported rightward more quickly than the kind A, and both

concentration profiles present breadth with time from drawing 12 B-E. It is clear that a seed is separated, in order that a concentration peak may be divided more quickly than breadth of a concentration profile and may move.

[0117]

5.3.2. Depend for the optimal selection of an operation parameter of a selection method of an optimal parameter, and a design parameter of a device on which [of the separation characteristics of particles] is optimized. This section explains a method for minimizing separation time by a desirable model. Probably, it will be clearer same method is applicable also to a realistic device model than having incorporated a device, potential, and structure with more detailed many about a particle transfer. In addition, the person skilled in the art can also optimize other separation characteristics, such as spatial distance of separation, using a similar method by desirable model and a more complicated model, for example.

[0118]

A desirable operation parameter is chosen so that all the separation time decided by cycle time $t_{on}+t_{off}$ of potential may be minimized. This section explains optimization of t_{off} and a related parameter to the 1st optimization of t_{on} and a related parameter, and the 2nd.

[0119]

A parameter selected by these methods is inevitably approximate. From a parameter of a statement, a more exact optimal parameter can be determined in this specification determined by the usual experiment using a actual device. It is not necessary to operate a actual device using an exact optimal parameter determined by arbitrary methods.For example, probably, a person skilled in the art understands that a actual device can be operated using parameter [optimum value / exact] shifted slightly or considerably, taking the characteristic of an available device, an error of setting out of an operation parameter, etc. into consideration. In order to acquire an optimum state, it is only said that it is preferred to operate a device in a place near a determined parameter.

[0120]

A method of a statement in this specification can be performed as a computer program by performing the usual conversion to suitable computer languages, such as C, Basic, and FORTRAN. Instructions can be given to a general-purpose computer system by this computer program, and a parameter selection method of a statement can be performed. As such a computer system, IBM PC or PC equivalent to it is mentioned, for example.

[0121]

It is preferred to choose a parameter of operation and a device so that it may become [whether t_{on} and desirable optimization t_{on} of a related parameter are made and] small. Here, in order to determine first an expression of relations showing relation between t_{on} and a related

parameter as the 1st according to a desirable model and to determine optimal value about these parameters as the 2nd, these expressions of relations are used.

[0122]

Time t_{on} is time for a charged particle to carry out the drift of [to the minimum which follows a separating direction at it from the maximum which can be set potentially (i.e., distance L-R)] under potential influence. For example, in drawing 10, t_{on} is time for particles to carry out a drift from 1001 to 1003. This time is obtained from the following formula.

[0123]

[Equation 9]

$$t_{on} = (L-R)/V_{drift}. \qquad (9)$$

V_{drift} is the drift velocity of the particle which can be set potentially among a formula.

[0124]

Since overdamping of the movement of the particles in a separation medium is carried out, V_{drift} is in direct proportion to what multiplied the power originating in potential by the coefficient of friction, and is calculated from the following formulas. : [Equation 10]

$$V_{drift} = \gamma Q\left(\frac{V_o}{L-R}\right). \qquad (10)$$

Here, since potential must be eccentric, please care about the point which are R<L/2. The electric field E in the suitable field of a drift is $-V_0/(L-R)$. The coefficient of friction gamma is connected as follows with a diffusing constant by the theorem of change-loss.

[0125]

[Equation 11]

$$\gamma = D/k_B T. \qquad (11)$$

For example, refer to the selection collected papers about Wax, ed, 15954, Selected Papers on Noise and Stochastic Processes noise, and stochastic process, Dover Publishers, and New York. t_{on} is calculated from the following formulas combining these formulas. : [Equation 12]

$$t_{on} = \frac{k_b T(L-R)^2}{QDV_o} \qquad (12)$$

Therefore, by the formula 12, since L-R is known, the minimum ****** can calculate most desirable t_{on}. V_0 should be chosen so that it may become a destructive electric field of the separation medium used and a residual electric field lower than an electrolysis threshold, and what is large in the ability to do consistent. It generates along with a potential more sudden side, and maximum electric field E_{max} is calculated from the following formula.

[0126]

[Equation 13]

$$E_{max} = \frac{V_o}{R} \qquad (13)$$

It should be made whether a device is made the optimal and to operate near the marginal electric field. In this case, t_{on} is calculated from the following formula.

[0127]

[Equation 14]

$$t_{on} = \frac{k_b T (L-R)^2}{QDRE_{max}}. \qquad (14)$$

In for example, the case of water. . A marginal destructive electric field is about 10^4V/cm. (Avallone et al.eds., 1987, Mark's Standard Handbook for Mechanical Engineers (Marks standard handbook for mechanical engineer), McGraw-Hill, and New York p15-19). Therefore, when it is R= 1 micrometer in $E_{max}=10^4$V/cm, a maximum of V_0 is 1V.

[0128]

In order to choose t_{off}, desirable optimization t_{off} of a related parameter, and a related parameter the optimal, it is necessary to specify what separating a particle type of the dispersion ratio D from a type of dispersion ratio D+delta D successfully means. In this section, deltaD is assumed to be far smaller than D. As for one desirable separation specification, at least, like breadth of a concentration peak, when large, separation of a difference in quitting time of a concentration peak of particles of two types from a device occurs. In this case, it is possible to distinguish a concentration profile of particles of two types by experience. Or in another expression, I hear that separation occurs in large time or the number of cycles like [position difference of a concentration peak of particles of two types] breadth of a gauss of at least two peaks, and it is. For example, by drawing 12 A, and 12B and 12C, if two

concentration peaks follow this desirable specification, it will not consider that they dissociate. However, it is considered in drawing 12 D and 12E that a peak is separated. In order to choose an operation parameter, it is also possible to use alternative separation specification which severity fluctuated somewhat. If severity is fewer conditions, it may be considered that drawing 12 C is what was similarly separated, for example.

[0129]

If this desirable separation specification is followed, separation will be generated in time t_D obtained from the following formulas. : [Equation 15]

$$\langle x_D(t_D)\rangle - \langle x_{D+\Delta D}(t_D)\rangle = \left[\langle \delta x_D^2(t_D)\rangle\right]^{1/2}, \qquad (15)$$

Here, after going through time [to be the time needed for the particles of the dispersion ratio D crossing a device] t_D, when a device is left, the concentration profile of the particles of two types is separated.

[0130]

From the formulas 5 and 6, a separating condition can be expressed as follows. : [Equation 16]

$$t_D f(\alpha_D - \alpha_{D+\Delta D})L = \sqrt{t_D f \alpha_D L^2 (1-\alpha_D)}, \qquad (16)$$

$alpha_D$ is probability which the particles of the dispersion ratio D diffuse to the following potential well between t_{off} among a formula. $alpha_D$ is calculated by the formula 7 shown here repeatedly for convenience.

[0131]

[Equation 17]

$$\alpha_D = \frac{1}{2}\mathrm{erfc}\left(R/\sqrt{4Dt_{off}}\right) \qquad (17)$$

From the formula 16, cycle several N_{cyc} ($=t_N f$) needed for separating the particles of the dispersion ratio D from the particles of dispersion ratio D+delta D is obtained from the following formula. : [Equation 18]

$$N_{cyc} = \alpha_D(1-\alpha_D)/(\alpha_D - \alpha_{D+\Delta D})^2. \qquad (18)$$

deltaD in which difference $alpha_D$-$alpha_D$+$delta_D$ is small enough - It can approximate as deltaDdeltaalpha$_D$/deltaD. The sum total separation time is as follows. : [Equation 19]

$$T_{tot} = N_{cyc}(t_{on}+t_{off}) \qquad (19)$$

Optimal desirable parameter is chosen so that T_{tot} may be made into the minimum. Operation and apparatus parameters are chosen so that t_{on} may be beforehand made into the minimum. Also indirectly, T_{tot} is influenced by t_{off} from N_{cyc} being dependent on $alpha_D$ influenced by t_{off} next at the same time it is directly influenced by t_{off} through the formula 19. In order to choose optimal value of t_{off}, all these formulas must be made into the minimum together. This minimization is most easily performed by trying various values about t_{off} systematically until a standard numerical method, for example, the minimum, is found out. For example, refer to Press et al., 1992, Numerical Recipes in C (numerical recipe of C), the 2nd edition, Cambridge Univ. Press, and New York. Optimal example of selection of t_{off} is described about a case of DNA fragment separation at Section 5.4.

[0132]

When optimal t_{off} and N_{cyc} value are chosen once, sum total device length needed for separation is obtained from the following formula. : [Equation 20]

$$L_{tot} = \langle x_D(t_D)\rangle = N_{cyc}\alpha_D L. \qquad (20)$$

Optimal desirable quantity chosen is influenced by potential spatial characteristic.

[0133]

In optimization of the above-mentioned of desirable optimization t_{on} of L and R, and t_{off}, it is assumed that R and L are being fixed.When such length can be fluctuated, these should be chosen in consideration of determination of optimal former time parameter. In consideration of the formula 14, L should be chosen [1st / doing / it / and] small first. Since 1/2 reduction of R enables reduction of 1/4 in t_{off} in consideration of the formula 17, R should be chosen [2nd / doing / it / and] small. In order to obtain sufficient eccentricity of electrode of a potential well to the 3rd, it is preferred that it is R/L<0.3. And R and L are restricted to a large thing by the 4th like the lower limit which selected production technology permits at least. A conflicting requirement about such R means that R optimal about a selected separation medium with fixed E_{max} (V_0 is changed) exists.

[0134]
In a desirable method for optimization, separation time T_{tot} is minimized as a function of L and R under constraints that size of a device obtained as a result can manufacture with selected production technology. As one additional constraints, there is a thing that it is optimal to choose potential V_0 applied so that an electric field may become smaller than destructive electric field E_{max} about values of L and R. It is chosen by optimal method so that T_{tot} optimal about fixed L and R which were given may be reached, as time t_{on} and t_{off} mentioned above for a value of this V_0. For a person skilled in the art of computer technology, multi-dimension minimization art which is a well-known thing is used (Press et al., 1992, and the 2nd edition of Numerical Recipes in C (numerical recipe of C)). Optimal pair of L and R is determined in an easy and desirable form from this optimization problem at Cambridge Univ. Press, New York, and this time.
[0135]
Optimal R may be determined in another method by simultaneous minimization within limits by which the formulas 14, 17, 18, and 19 were permitted technically. This can be performed by standard numerical art from Press et al. Or this optimization can be performed with the following simple retrieving procedures. The first stage R in the minimum tolerance level is selected, and optimum-value T_{tot} is determined by an above-mentioned method. For example, only that fractionation makes R increase by a little only 5%, and determination of optimal T_{tot} is repeated. The maximum of V_0 applicable to all the determination of T_{tot} in a given selected, fixed separation medium is chosen. With either the range of the lower one about R, or a mean value of R, it continues repeatedly [this] until the minimum of T_{tot} is discovered. A desirable value of R makes T_{tot} the minimum. When R is chosen, L can be determined so that R/L may have a fixed value which provides desirable sufficient eccentricity of electrode of a potential well. R/L is less than 0.3 and is about 0.1 more preferably.
[0136]
About all the following sample calculations, especially, as long as there is no notice, it is assumed that optimum values are R= 1 micrometer and L= 10 micrometers. Although potential with this periodicity is described by Section 5.5, it is easily generated by common micro production technology like.
[0137]
Finally, a separation medium should be chosen so that particles which should be separated may have a dispersion ratio which it is made to be suspended where electrification is carried out into a medium, and is different by suspended state voice. The more a difference of a

dispersion ratio becomes large, the more a medium will become desirable. It is preferred to be chosen from suitable media in respect of others so that a separation medium may have comparatively high E_{max} and comparatively high electrolytic voltage compared with other suitable media. Here, a word that it is comparatively high can be considered to mean ******** at least about a suitable medium in respect of others. These conditions permit minimum t_{on}. It is preferred to have low ionic strength finally, in order that a separation medium may make cover of a potential well minimum.

[0138]

5.3.3. When changing a dispersion ratio substantially, the above paragraph has described desirable operation in consideration of a desirable model and its model about a case where it has the dispersion ratio to which particles which should be separated were similar, and determination of apparatus parameters. A dispersion ratio can apply this invention also to a mixture containing particles changed substantially.

[0139]

There is one operation form for separating such a mixture in starting in the state of being in optimal brief time, in order that t_{on} and t_{off} may separate particles of a higher dispersion ratio. In such time, particles with a higher dispersion ratio are separated quickly. However, lower particles of a dispersion ratio have far small $alpha_D$ value, and remain in a state of rest mostly. after particles with a higher dispersion ratio are separated, time t_{on} and t_{off} are the optimal because of separation of lower particles of a dispersion ratio -- it depends and is increased to a big value. At this time, lower particles of a dispersion ratio are divided into urgency after that.

[0140]

Suitable longer t_{on} for lower particles and t_{off} time of a dispersion ratio are used for one operation form which will be accepted in order to separate such a mixture. In such longer time, higher particles of a dispersion ratio have bigger $alpha_D$ value, and can have the capability to make a forward direction and an opposite direction diffuse two or more potential wells. Please assume that it is whether particles which should be separated moved, or to have diffused at most one potential well in t_{off} in a forward direction in the above-mentioned model. However, about a case where some of particles which should be separated diffuse two or more potential wells in t_{off}, a similar model based on a random walk accompanied by a drift can be built.

[0141]

In order to build such a model, particles of the dispersion ratio D define $alpha_D^{(n)}$ as probability of diffusing n potential wells, in time t_{off} for free diffusion. If a standard divergence theory is followed by a method similar to the formula 7, these alpha will be obtained from the following

formulas.

[0142]

[Equation 21]

$$\alpha_D^{(n)} = \frac{1}{\sqrt{4\pi D t_{off}}} \int_{R+(n-1)L}^{R+nL} dx \exp(-x^2/4Dt_{off}). \qquad (21)$$

In $alpha_D^{(1)}$, the dispersion ratio D approaches the value of $alpha_D$ of the formula 7 quickly, when comparatively small compared with t_{off}. In this case, $alpha_D^{(1)}$ and $alpha_D^{(0)}$ (probability which remains in the state where particles were placed), It is only non-zero $alpha_D^{(n)}$, and this means being whether it remains in the state where particles were placed, or to diffuse only the interval of a single potential well in a forward direction. However, when a dispersion ratio is comparatively large, $n=-_D$ [about 1 2, etc. / alpha] (n) will be able to become large.

[0143]

When particles can diffuse two or more potential wells in t_{off}, in order to carry out the modeling of the invention, parameter $alpha_D$ is defined as diffusion length with effective high probability, and is done again.

[0144]

[Equation 22]

$$\alpha_D = \sum_{n=-\infty}^{\infty} \alpha_D^{(n)} n. \qquad (22)$$

In this definition, the average position of the maximum Mr. Gauss's particle concentration profile called $<x_D(t)>$ also here is searched for by the following formula. : [Equation 23]

$$\langle x_D(t) \rangle = tf\alpha_D L \qquad (23)$$

This is the same as the formula 5 of the above-mentioned model assumed that particles diffuse at most one potential well.

[0145]

Dispersion in the Gauss Mr. particle concentration profile of the particles of the dispersion ratio D after the total time t called $deltax_D$ (t) also here is after that. [Equation 24]

$$\left\langle \delta x_D^2 \right\rangle = \left\langle x_D^2 \right\rangle - \left\langle x_D \right\rangle^2 = \sum_{n=-\infty}^{\infty} \alpha_D^{(n)} n^2 L^2 - \alpha_D^2 L^2 \qquad (24)$$

It is equal to what varied about a ********** single cycle and multiplied the number of diffusion cycles within the time t to be tf by change <deltax$_D^2$>.

[0146]

Distance between concentration peaks of desirable conditions which define also here generating of separation of particles of the dispersion ratio D from particles of dispersion ratio D+delta D to which deltaD expresses a size more than D in this case again must be a size more than half of width of a concentration profile. This condition for separation is acquired from the formulas 23 and 24 from the following formula.

[0147]

[Equation 25]

$$N_{cyc} L \left| \alpha_D - \alpha_{D+\Delta D} \right| = \sqrt{N_{cyc} \left\langle \delta x_D^2 \right\rangle}. \qquad (25)$$

These formulas enable the conclusion same about this case where deltaD is about D or more as well as the case of the above-mentioned which is deltaD<<D. The formulas 21 and 23 have proved that particles with a larger dispersion ratio are transported through a device more quickly than the particles of a smaller dispersion ratio, and that the distance between concentration peaks increases linearly with time as above-mentioned. The formula 25 has proved that the peak of a different dispersion ratio is separated. Since the distance between concentration profiles increases linearly with N_{cyc} only to increasing as a square root of N_{cyc} by the width of a concentration peak also here again, separation occurs. Separation time is decreased by 1/4 every 1/2 in potential space scales reduction for the action of the formula 21.

[0148]

An operation parameter which furthermore optimizes t_{on} can be chosen by the above-mentioned case and a similar method. For example, N_{cyc} is calculated by the following formula. : [Equation 26]

$$N_{cyc} = \frac{\sum_{n=-\infty}^{\infty} \alpha_D^{(n)} n^2 - \alpha_D^2}{(\alpha_D - \alpha_{D+\Delta D})^2} \qquad (26)$$

This corresponds to the gestalt of the formula 18. Therefore, t_{off} which makes T_{tot} the minimum can be obtained by numerical minimization of the formulas 19, 21, 22, and 26 in a form similar to the above-mentioned case where particles diffused at most one potential well in t_{off}.

[0149]
Thus, even when an operation parameter is chosen so that particles with a higher dispersion ratio may diffuse two or more potential wells in t_{off}, it is possible to separate the mixture of particles in which a dispersion ratio is changed substantially by this method. In one operation form for separating such a mixture, Cycle time t_{on} and t_{off} can be gradually increased to a big value rather than it made it optimize first for rapid separation of the higher particles of a dispersion ratio and having been optimized for the separation of the lower particles of a dispersion ratio to the next. In the 2nd operation form, it is possible to make cycle time optimize so that the maximum fragment may be separated, and to provide the suitable separation for a still in addition more small fragment.
[0150]
5.3.4. alternative -- also acquire a state of operation form:a large number and one operation form consists of carrying out the cycle of the potential not through two states but through three states. These three states change :1. potential including the following stages to one.;
2. Reverse 1 time or multiple-times potential short between on-conditions.;
3. Make free diffusion possible.
[0151]
between on-conditions -- potential -- 1 time or multiple times -- when reducing electrostatic shielding from an ion double layer formed with a counter ion with high small **** mobility drawn to a potential well or an electrode, it is effective to make it reversed brief and it obtains. By making t_{on} scattered to some high-speed pulses reversed by potential polarity, these counter ions can be moved and a double layer can be made into the minimum. An inversion cycle is small enough so that a smaller counter ion with high mobility of that which is substantial completely uninfluential to distribution of lower particles of desirable more large mobility may be moved to an opposite direction from outside from a potential well, or an electrode. This is attained by filling inequality $t_{pulse} << t_{on}$ and t_{off}.

[0152]

In another tri-state operation form, the 3rd state suddenly and substantially accompanied by symmetrical V type potential centering on a bottom of each potential well which can be made by the 3rd electrode between 2 sets of electrodes which exist in a device of Types I and II is used. An electrode of this embodiment is the periodicity L and is a relative location. - It is positioned by R, O, and R. In the 1st state of continuing only time t_{on}, electrification of the electrode in the relative location O is carried out to $V_0/2$, and electrification of the electrode in the relative location R is carried out to $-V_0/2$. In the 3rd state of continuing only time t_{off}, as for an electrode, all electric charges are removed, and particles are diffused freely. These 1st and 3rd states are the same as two states of an operation form described in the above-mentioned paragraph. In the 3rd additional intermediate state, it is a relative location. - Electrification of the electrode in R and +R is carried out to $+V_0/2$, and electrification of the bipolar electrode in the relative location 0 is carried out to $-V_0/2$. In this way, a potential well of narrow V type which localizes particles densely is made.

[0153]

This is a useful thing from the ability to provide a stronger more narrow trap for particles at a bottom of a potential well which has a sudden wall in the either side. This will generate near density distribution according to thin desirable distribution to about [which is not almost in each well in each potential cycle].

[0154]

5.3.5. Other embodiments : when other embodiments carry out the lamp of the temperature of a device, or change it to a thermal light pan during operation and movement and separation take place preferably, include raising temperature. This mode is advantageous to separating a particle group which has a wide range diffusion coefficient, and can also be carried out combining a mode indicated to Section 5.3.3. In low temperature, since particles, such as a molecule, have typically low diffusibility (refer to formula (27)) and a fluid to accommodate has typically high viscosity, movement and separation of motile high particles and a molecule are performed more by such low temperature. In an another side elevated temperature, since particles have typically high diffusibility (refer to formula (27)) and a fluid to accommodate has typically low viscosity, movement and separation of motile low particles and a molecule are performed more by such low temperature. In this embodiment, temperature of a device is made low, motile high particles in a sample are made to separate more, temperature of a device is made high behind and motile low particles are made to separate in the first time interval more.

[0155]

In more detail, the lamp of the temperature can be carried out by two or more steps, it can be raised, and can also be raised continuously. A part for a temperature increase can be

determined as the motility of a motile low kind changes with about 1.2, 1.5, 1.8 and 2.0, or the coefficients beyond it more. separation of a single stranded DNA -- the melting point of a solvent -- exactly -- a top to the boiling point -- temperature can be exactly raised to lower. Especially, in a solution near solution or solution, temperature can be raised from about 4 ** to about 97 **. Thus, 50 in a sample and a DNA molecule of 51 base pairs are separable from DNA of 300 and 301 base pairs, for example. The above-mentioned temperature control module can perform a thermal light or a temperature change.

[0156]

An embodiment of further others is realized by adjusting dynamically other conditions of determining particle moving speed. Inclination **** or solvent programming is included in these conditions. D. -- A.Skoog and f.J., [Holler and] On and T.A.Nielman, 1998, Principles of Instrumental Analysis, 5thed., and a Saunders College Publishing general target. All art applicable to improvement in chromatography separation is applicable to a decollator of this invention.

[0157]

5.3.5. other embodiment: -- a voltage lamp -- other additional embodiments are a potential run ping under operation of a device, or change. Although it is too quick for the greatest molecule fragmentation following in this mode of this invention, sufficient cycle time for smaller fragmentation to follow is used potentially. In such a case, separation takes place as a result of a different reaction to a voltage run ping by fragmentation of a different size.

[0158]

Separation takes place by changing potential on high drive frequency first especially. This frequency is first set so that separation of the minimum and fastest particles may be optimized. This frequency falls continuously or intermittent gradually. The minimum fragmentation moves the length of a chip by this, and bigger fragmentation follows this. Fragmentation which has the same size reacts to same voltage variation, and separation takes place. Speed of a frequency drop can be optimized for desired separation, if a diffusion rate of a kind to separate is given. Although there is no reliability in isotropic diffusion of a molecule to separate, separation is still based on molecule speed in carrier fluid depending on a size and mass.

[0159]

In this approach, an adjoining electrode pair is not connected mutually. Rather, as for voltage, the length part sweep of the chip is carried out in inside of a progressive wave. Unlike fragmentation low-mass smaller more, the fragmentation with mass large larger more cannot follow this wave. If fragmentation smaller than once comes out of a detection area of a chip, frequency of a progressive wave is reduced and can follow slightly bigger fragmentation than it. This is repeated until all the object fragmentation is detected.

[0160]

For example, the size r considers a device 0.1 micrometer and whose voltage gap of an ON state are 0.1V to be a mixture of a DNA fragment of the range of 20 - 200bp. In order to separate 20mer from 21mer, in a specific embodiment, consider it as frequency for 1-10 kHz, and most preferably, It is an ON state during a $1.5x10^{-4}$ second, and an OFF state during a $2.2x10^{-5}$ second, and continues for 1.4 seconds ($D=8.14x10^{-7}cm^2$ / second, and $7.91x10^{-7}cm^2$ / second were used for calculation, respectively).

[0161]

Most preferably, in order to separate 201mer to 200mer, it switches to an ON state during a $5.5x10^{-5}$ second, and an OFF state during a $6.5x10^{-5}$ second continues for 100 seconds.

[0162]

5.4. There is an important field of the invention of application this invention to DNA separation in separating a biopolymer (a biopolymer fragment is included), especially nucleic acid like DNA (for example, cDNA, genomic DNA, a synthetic DNA) and RNA. Since a dispersion ratio of DNA is influenced almost extensively by the number of nucleotides in a DNA molecule, use in this field is attained. Although it is not substantial, the dependency of a dispersion ratio to a ratio of A+T versus G+C also exists about sum total base composition, i.e., dsDNA.

[0163]

Separation resolution needed changes with fields of the invention of DNA separation, and results [from resolution of a single base pair] even in large resolution called not less than 10% of sum total DNA length. For example, generally for DNA sequence determination which is a field of the invention which probably has ****** familiarity, DNA must be separated with resolution of a single base or a base pair. It does in this way, By a standard sequencing reaction. An aliquot (for example, F.Sanger.) of generated DNA It is possible to give et al., 1977, Proc. Natl. Acad. Sci.USA74;5463;M. Maxam et al., 1977, and Proc. Natl. Acad. Sci.USA74:560 to a separation method of this invention. In another field of the invention of DNA separation called size evaluation (sorting), only **5% or **10% of resolution of fragment length is needed. Size evaluation is used in order to generate promptly a pattern or a fingerprint of size in a DNA mixture by which it is generated for a field of the invention of RFLP determination, genotype determination, chain analysis, microsatellite analysis, and other fragment analysis and in which it deals.

[0164]

5.4.1. A diffusing constant of ssDNA used for dispersion ratio operation of DNA and selection of apparatus parameters and dsDNA can be presumed from a principle of a stokes, or can be obtained by experiment. A diffusing constant of particles of a principle of a stokes is obtained from the following formula. : [Equation 27]

$$D=k_BT/6\pi\eta\Gamma, \qquad (27)$$

Temperature and eta among a formula T The viscosity of a separation medium (about water, it is a 0.01 gm/cm second), gamma is an effective particle radius (Doi et al., 1986, The theory ofPolymer Dynamics, Clarendon Press, Oxford, p300).

[0165]

About globular form particles called the denaturation ssDNA, gamma is identified as a turning radius. The scaling theory has connected the contour length and the turning radius of ssDNA like a polymer. general -- index gamma as 0.6 -- gamma-N it is (for example, Doi et al. -- refer to the above). About the long cylinder which is the a>> diameter b as it was called dsDNA, it turns out that it is gamma a/ln (a/b). In dsDNA with N base pairs, the diffusing constant of the principle of the stokes accompanied by this approximation is called for from the following formulas. : [Equation 28]

$$\frac{1n(a/b)k_BT}{3\pi\eta a} = (1/N)1n(0.3N) \; X \; 1.5*10^{-5}cm^2/s \qquad (28)$$

It is b= 10A in diameter among a formula, and is length a=3NA. The temperature T is assumed to be 298degreek through the whole.

[0166]

An empirical formula about a diffusing constant is preferred, and, below, this is used through the whole. A dispersion ratio of dsDNA in an underwater room temperature is approximately called for by experiment from the following formulas. : [Equation 29]

$$D_{dsDNA} = 1.14 \times 10^{-6}N^{-1}cm^2/s \qquad (29)$$

N is the number of base pairs among a formula (Weast, ed., 1987, Handbook of Chemistry and Physics, Chemical Rubber Publishing Co, Boca Raton, floor line, p117). The reverse dependency over N is governing the comparatively weak 1n (N) paragraph in the formula 31 on observation. About ssDNA, it is assumed that a dispersion ratio is theoretically obtained from the following formula.

[0167]

[Equation 30]

$$D_{ssDNA} = 1.14 \times 10^{-6}N^{-0.59}cm^2/s \qquad (30)$$

Scaling in N is deduced from the principle of the stokes which predicts that D is influenced by the reciprocal of an effective radius. An effective radius is deduced from considering that ssDNA diffusion resembles self-evasion Wolk by whom an effective radius is influenced by the number of bases $N^{0.59}$. For example Refer to Doi et al. and the above.

[0168]

the optimal selection of 5.4.2t_{on} and t_{off} -- t_{on} which is time required to attract a DNA fragment in the desirable determination potential well of optimal t_{on}, It can determine by combining the formula 12 about t_{on}, or the formulas 29 and 30 about the diffusing constant of 14 and DNA. The electric charge Q on DNA is [ssDNA] -2 N|e-| about -N|e-| and dsDNA, N is the number of a base or base pairs here, and |e-| is an absolute value of electronic charge. t_{on} is calculated from the following formulas using V_0 of a bolt unit, and (L-R) of mum unit. :

[Equation 31]

$$t_{on} = \frac{(L-R)^2}{(V_o/2)N^{0.41}} \times 1.1 \times 10^{-4}\,\text{sec}, \quad ssDNA; \qquad (31)$$

[Equation 32]

$$t_{on} = \frac{(L-R)^2}{(V_o/2)} \times 5.6 \times 10^{-5}\,\text{sec}, \quad dsDNA; \qquad (32)$$

When V_0 is chosen as a break down voltage of water, t_{on} is obtained from the following formulas as that L and whose R are mum units. : [Equation 33]

$$t_{on} = \frac{(L-R)^2}{RN^{0.41}} \times 2.3 \times 10^{-4}\,\text{sec}, \quad ssDNA; \text{ and}$$
$$t_{on} = \frac{(L-R)^2}{R} \times 10^{-4}\,\text{sec}, \quad dsDNA, \qquad (33)$$

Table 2 shows t_{on} of the second bit about the device in L= 10 micrometers, R= 1 micrometer, and V_0=1V. About the high-speed desirable separation, t_{on} should be chosen as a thing small in the ability to do.

[0169]

[Table 2]

フラグメントサイズ	t_{on} for ssDNA (secs)	t_{on} for dsDNA (secs)
10	0.0071	0.0091
100	0.0028	0.0091
500	0.0014	0.0091

Scaling of the time t_{on} is linearly carried out with potential space scales (R and L). Scaling of this is carried out in a form which is different with N about ssDNA and dsDNA. Although driving force increases linearly with molecule length about ssDNA, since a dispersion ratio decreases more at a low speed, t_{on} is a decreasing function of molecule length. About dsDNA, since the dependency of driving force to molecule length cancels the dependency of a dispersion ratio to fragment length correctly, t_{on} is unrelated to molecule length.

[0170]

a desirable determination of optimal t_{off} -- preferably, optimal t_{off} is selected so that sum total separation time T_{tot} may be made into the minimum. T_{tot} is obtained by combining the formula 19 about T_{tot} with the formula 18 about N_{cyc}.

[0171]

[Equation 34]

$$T_{tot} = (t_{on} + t_{off}) \alpha_D (1-\alpha_D) / (\alpha_D - \alpha_{D+\Delta D})^2. \qquad (34)$$

The dependency of $alpha_D$ to D and t_{off} is acquired from the formula 7, and this is shown here repeatedly.

[0172]

[Equation 35]

$$\alpha_D = \frac{1}{2} \mathrm{erfc}\left(R/\sqrt{4Dt_{off}}\right) \qquad (35)$$

D is influenced by N which is a base in DNA which should be separated, or the number of base pairs according to the formulas 32 and 33.

[0173]

In order to make T_{tot} into the minimum, parameter t_{off} is systematically fluctuated so that it may obtain the minimum about T_{tot}. Parameter t_{off} is selected in the optimal form so that it may become a value which makes T_{tot} the minimum.

[0174]
An example program in the C language for calculating a parameter of DNA separation for this invention according to these expressions of relations, especially the formulas 33, 34, and 35 is described by Section 8. Selection between the length R and L, length [about a DNA molecule which should be separated] N and N+deltaN, ssDNA, and dsDNA is included in an input. The voltage VO is automatically selected so that it may become superfluous potential by which a destructive electric field of water and electrolysis of water are generated, and the consistent maximum. A program can be changed about a value of these suitable parameters for other separation media. A program fluctuates t_{off} systematically in order to find out optimal T_{tot}. Further details of operation containing optimal operating condition t_{on}, t_{off}, N_{cyc}, and T_{tot} are included in an output. A file which contains a value of such quantity in within the limits around an optimum value is similarly included in an output. This program can be compiled and executed on all computer systems that carry out entailment of a C language compiler and the run time system. If it is a person skilled in the art, this program can be translated into such a language for execution on a computer system with other similar languages.
[0175]
Drawing 13 shows an example of the optimal selection of t_{off} which used a program. T_{tot} is numerically evaluated using t_{off} about potential into which a dsDNA molecule of the length 100 will be separated from a thing of the length 105 in an aquosity separation medium and which has L= 10 micrometers and R= 1 micrometer. Drawing 13 shows a graph obtained as a result about a relation between these two quantity. It is clear that the optimal selection about t_{off} is 0.10 second, and this produces optimal sum total separation time for 6.8 minutes from drawing 13.
[0176]
Table 3 has presented a result of similar optimization about various DNA molecule length and separation resolution needed. In all the cases, separation is the potential which has L= 10 micrometers and R= 1 micrometer, and is a thing in inside of an aquosity medium.
[0177]
[Table 3]

DNAフラグメント	T_{tot}/ 分	L_{tot}/cm	t_{off}/ 秒	N_{cyc}	α_N
ssDNA					
$N=10,\Delta N=1$	0.48	0.083	0.0053	2.3×10^3	0.036
$N=100,\Delta N=1$	71.	4.4	0.015	2.3×10^5	0.019
$N=100,\Delta N=10$	0.85	0.057	0.016	2.7×10^3	0.021
$N=500,\Delta N=25$	7.0	0.18	0.038	1.1×10^4	0.017
$N=500,\Delta N=50$	1.9	0.052	0.039	2.8×10^3	0.019
dsDNA					
$N=10,\Delta N=1$	0.32	0.028	0.013	8.7×10^2	0.032
$N=100,\Delta N=1$	150	1.48	0.098	8.5×10^4	0.017
$N=100,\Delta N=10$	1.9	0.021	0.11	9.9×10^2	0.022
$N=500,\Delta N=25$	32.	0.067	0.50	3.8×10^3	0.018
$N=500,\Delta N=50$	9.0	0.020	0.52	1.0×10^3	0.020

Drawing 14 shows an abstract of a majority of such optimizing calculation in a graph. A horizontal axis of a graph expresses desirable separation resolution expressed as a percentage of molecule length. A vertical axis expresses necessary sum total separation time T_{tot} of a minute unit. A graph shows separation time needed for the two molecule length 100 and 500 about ssDNA and dsDNA. All the separation is the things in inside of an aquosity medium also here again by potential which has L= 10 micrometers and R= 1 micrometer.

[0178]

In size evaluation for which separation needs only 5 to 10% of resolution from drawing 14 compared with a case of sequencing which needs 1% or less of resolution, it is clear that it is a high speed far. From drawing 14, change by a coefficient called 10 of resolution needed draws change by a coefficient called 100 of T_{tot}. For example, separation of a molecule of the length 100 by resolution (5%) of five bases can be performed 25 times as quickly as separation of a molecule of the length 100 by resolution (1%) of one base. Therefore, when this device is used, it turns out clearly that sequencing with quick DNA and very quick size evaluation are possible. For example, if size of a device is reduced and a dispersion ratio is increased by changing a separation medium or raising temperature, separation time of the device will be shortened.

[0179]

5.4.3 - potential eccentricity of electrode -- this section describes the example of an actual proof of saying [that potential with high eccentricity of electrode becomes more desirable as separation time becomes quick]. The optimal separation parameter is calculated about the potential to which the potential well of a thing with the fixed cycle length L of 10 micrometers and the distance R between the nearest adjoining maximums are changed. A smaller R/L ratio means that the potential minimum is placed by the inside of each potential well with high

eccentricity of electrode. Table 4 shows the result of the calculation performed with the single base resolution (1%) in an aquosity medium for separation of the ssDNA fragment of the length 100. V_0=2V is used in all the cases.

[0180]

[Table 4]

R/μm	T_{tot}/分	L_{tot}/cm	t_{ot}/秒	N_{cyc}	α_N
2	246.	4.0	0.058	2.5×10^5	0.016
1	66.	4.2	0.015	2.4×10^5	0.017
0.5	21.	4.9	0.0041	2.3×10^5	0.022
0.25	9.5	6.5	0.0012	2.0×10^5	0.032

The performance of a device increases as a R/L ratio decreases. That is, sum total separation time decreases.

[0181]

5.5. The device which operates in accordance with the method of micro manufacture this invention of the device of Types I and II may be suitable for the field of the invention of separation, and may be a thing of the minimum size moreover mentioned above and what kind of consistent physical size. In a desirable embodiment which is separated [whether the biopolymer fragment in which electrification of the device was carried out is made, and] at high speed, as for physical size, as long as the separation medium by which production technology approved and was generally meant allows, it is preferred that it is small. In this section, the example of the manufacturing method which used standard micro production technology is introduced about the device of the types I and II suitable for the aquosity separation medium by which about 2-volt potential difference is applied. Since this invention carries out entailment of the device of the size of the manufacture and others according to other art, these methods are only examples.

[0182]

The sizes of the example of a device of Types I and II are about 1 cm - 10 cm in accordance with a separation axis, and are about 1 cm - 10 cm in a transverse direction to a separation axis. the separation between the channels which as for about 30-50 micrometers in width and a depth of 10 micrometers the channel in a device comes out, is isolated every 100 micrometers, and adjoin is about 50 micrometers. About 20 micrometers of electrodes in two or more sets each are isolated, namely, it is L= 20 micrometers, and width is about 0.8-1 micrometer. The electrode in two or more sets each is mostly moved relatively by only the part of the width. Namely, R= 0.8-1.0 micrometer. The electrode in two or more sets each is connected to the electrode pad at the edge of the device for the link to an external voltage source.

[0183]
Except for the case where there is a statement, the following micro manufacturing planning is equally applied to the device of both types. The substrate with a method preferred for 5.5.1. board this device which is standard in micro production technology (Sze, 1988, VLSITechnology, McGraw Hill, New York) described, It is glass like soda lime glass. As an alternative substrate, plastics, such as fused silica, a borosilicate, quartz, Pyrex (registered trademark) and polymethylmethacrylate, polycarbonate, polystyrene, and polyimide, are mentioned. The sizes of a glass substrate are about 1-10 cm x 1-10 cm, and thickness is 1-5 mm. The suitable supply source of a glass substrate is the microscope slide of soda lime glass, for example, a 75x50x1-mm slide, (Fisher Scientific catalog number 12-550C).
[0184]
In addition, a substrate must be purified in advance of all the micro manufacturing stages. This makes a substrate immersed into the hot bath of H_2SO_4/H_2O_2 about a glass substrate, It can carry out by washing in H_2during 10 minutes O, washing by H_2O again, and removing the water adsorbed by drying for 10 minutes in about 150 ** oven.
[0185]
5.5.2. The electrode for an electrode manufacturing installation can be manufactured from various metal. Desirable metal is aluminum, Ag, Au, and Pt. Although aluminum is advantageous at the point which can use an available CMOS foundry easily, this is disadvantageous at the point of being easy to receive electrolysis deterioration compared with the precious metals. Other metal containing Ti, nickel, Zn, Ru, Pd, Ta, W, and the doped polysilicon can be used for the electrode of a device. It is the 2nd alternative suitable for the 1st alternative and Au suitable for :, i.e., the 1st method that was suitable for all the desirable metal using etching, the alternative electrode manufacturing method for these metal is described to be, and Pt.
[0186]
The pattern mask for photo lithography is manufactured in advance of the electrode manufacture using the 1st method or 1st alternative way. Drawing 15 has illustrated an example of a mask. An electrode which is in 1501, 1502, 1503, and 1504 is substantially arranged in the transverse direction to the separation axis S. Each electrode is about 1 micrometer in width. An electrode forms two or more two sets, and the electrode of each set is connected to one of the electrode pads 1505 and 1506. These pads are about 0.1 mm on a scale of macroscopic, and serve as a point of contact to an external voltage supply. Spacing of the electrode two or more sets each is periodically carried out in the distance L, it receives mutually, and is moved by only the distance R. The mask of these sizes can manufacture easily using a standard micro lithography technology. For example, a suitable mask is obtained by removing selectively the chromium laminated on the quartz surface. Chromium is removed

using the computer-aided design which provides an input for a pattern generation program, for example. available -- if it becomes --; with the preferred smaller feature size -- the size used here is only an example.

[0187]

The 1st method for manufacturing an electrode begins from making a layer with an equivalent thickness of 1 micrometer of metal selected on the side of the substrate which should support an electrode laminate. The metal layer can be about 1 micrometer from about 100 nm, and may be 300 nm preferably. Metal can be made to laminate by a physical vapor deposition, chemical vacuum deposition, or sputtering. At this time, spin coating of the positive type photoresist is carried out on a metal layer, and soft bake is stable. The feature on a mask is transferred by photoresist by irradiating with UV light, and the non-protection location exposed by light is dissolved with a suitable solvent. The photoresist to continue is fixed to a predetermined place by the hard baking powder in an elevated temperature.

[0188]

An electrode is generated by etching the metal field which is not protected by photoresist. About an Al electrode, etching can be attained by exposing the surface with Cl_2 steam. Cl_2 molecule reacts to the Al atoms on the surface, and generates $AlCl_3$, and this $AlCl_3$ separates from the surface for volatility. About Au and an Ag electrode, in order that an undercut may destroy the electrode of mum scale, wet etching is not preferred. These features are preferably etched using Ar+ ion milling. In this method, it is accelerated into the surface and Ar+ ion from Ar radio frequency plasma causes etching by a physical impact. It becomes possible to manufacture the electrode accompanied by the straight side attachment wall which maintains a mask size by milling.

[0189]

The remaining photoresist is removed from the surface of a substrate after etching, and the surface which supports an electrode is purified for subsequent processing.

[0190]

Standard micro machining technique is used for the 1st alternative way suitable for Pt electrode. This method is suitable also for Ru and Pd electrode again. Manufacture begins from covering of 10-nm-thick Ti which used the evaporation system. This Ti layer acts as a subsequent Pt layer and an adhesion layer between glass. Next, a 100-nm-thick Pt layer is made to cover the upper surface of Ti using Ar ion sputtering system. An electrode is constituted in a metal layer using photo lithography and etching. This process carries out the spin coat of the photoresist to the upper surface of Pt, and begins from exposing photoresist to UV light through the photo lithography mask which has an electrode pattern upwards. Next, the exposure part region of photoresist can be dissolved in a developer, and it can remove, and can leave the unexposed field which constitutes an electrode pattern. The remaining portion of;

metal which will protect the region of the metal in which photoresist should be held is removed using ion milling. In a milling process, it is accelerated electrically, and Ar+ ion by which electrification was just carried out collides on the surface of metal, and corrodes a layer physically. Once this etching is completed, it will dissolve with acetone and photoresist will leave the finished electrode.

[0191]

The micro adhesion burning method (muCP) is used for the 2nd alternative way suitable for Au (Xia etal., 1995, and J.Am.Chem. Soc.117:3274-3275;Jackman et al., 1995, Sciece269:664-666). The elastomer stamp made instead of the photo lithography mask according to the same pattern of the same size is used. Drawing 16 A-B shows the example of a pattern. A stamp can be manufactured from poly dimethylsiloxane. You are made to laminate Au on the surface of a substrate like the above-mentioned thing using a standard method by thickness of 1 micrometer. Next, an elastomer stamp is made humid by an alkane thiol, and is pushed against a gold surface. A suitable alkane thiol is $CH_3(CH_2)_{15}SH$ (Kumar et al., 1994, Langmuir10:1498-1511). Although spreading by which the patternized self-collapsible alkane thiol monolayer on a gold surface was controlled can be attained by performing underwater baking, there is an advantage of contracting the feature size in the form which can further be predicted in this. A stamp and a substrate are removed from water, and are dried using N2 gas, and then a stamp is removed from a substrate. Unprotected gold is removed by making it immersed into cyanide fluid (KCN of 0.1M, KOH of 1M), agitating violently using air or oxygen as an oxidizer (Kumar et al., above). After fully rinsing, an alkane thiol is removed from the surface and two or more sets of gold electrodes are generated.

[0192]

5.5.3. The channel of the channel manufacture type I device of the device of Type I can be manufactured by carrying out wet etching of the glass substrate. A photo lithography mask must be built in advance of channel manufacture. Drawing 16 A shows one example of a mask. If a channel is not so, as it is on an opaque mask 1601 and 1602, it is constituted by the transparent muscle. The width C of each muscle deducts all the undercuts expected in an etching process from desirable channel width. About the process described, since an anticipation undercut is 8-10 micrometers, a 40-micrometer-wide muscle manufactures the channel whose desirable final width is 55-60 micrometers. The width W between muscles adds all the undercuts expected by the desirable channel interval.

[0193]

Drawing 16 B has illustrated alternative channel geometrical form. A channel called the channel 1606 is converged here from the large interval of a load zone expressed with 1603 as a whole to the narrow interval of the detection zone shown by 1605 as a whole. Since the interval in the load zone 1603 is large, a channel becomes possible [accommodating an

injection port called 1604 of a larger diameter than the desirable interval between channels]. Although drawing 16 B has illustrated the fragment-like straight-line channel, the alternative channel geometrical form of a curve can also be fitted to this invention, for example.

[0194]

A suitable photo lithography mask can be manufactured by removing selectively the chromium laminated on the quartz surface. For example, chromium is removed using the computer generation design which serves as an input to a pattern generation program.

[0195]

Channel manufacture begins from carrying out the spin coat of the positive type photoresist on a glass substrate. Expose a substrate with a hexamethyldisilazane steam for 5 minutes, and a spin coat is carried out by photoresist (Microposit S1400-31, Shipley, Newton, MA), Suitable photoresistor is generated by stabilizing photoresist by heating at 90 ** for 0.5 hour. A mask is aligned over the coated whole glass substrate, and a pattern is stamped on photoresist using UV light. The field of the photoresist exposed by UV light dissolves (1:1 mixtures of H2O and a Microposit developer concentrate, Shipley), and the photoresist to continue is fixed by baking at 150 ** for 1 hour.

[0196]

Or a channel can also be constituted in a glass substrate using a Cr layer. This process starts by evaporating a 100-nm-thick Cr layer on glass. The Cr layer covering the whole lane which should be manufactured is removed using photo lithography and etching at this time.

[0197]

Next, wet etching of the non-protecting part region of a substrate is carried out by exposing the surface of a glass chip to aquosity NH_4 / HF etching solution (1:1 mixtures of BOE5:1 and BOE10:1, J.T.Baker, Phillipsburg, NJ). By etching for 20 minutes, a 10-15-nm-deep channel is manufactured, and the undercut of every 8-10 micrometers of the photoresist is carried out by each side. Therefore, the feature size of 40 micrometers on the mask for patternizing generates the channel of illustration width as 55-60 micrometers. In the case of glass, photoresist or a Cr layer is removed from a substrate after etching by clarification which used the above elevated-temperature H_2SO_4/H_2O_2, for example.

[0198]

5.5.4. The channel for the channel manufacture type II device of the device of Type II is preferably manufactured by the upper surface of an electrode. Or these channels can also be manufactured on the upper surface of other substrates. A suitable photo lithography mask is manufactured first. Generally such a mask is similar with the case of the channel of the device of Type I except for the following three points. That is, this mask constitutes two channel walls which form the muscle of each channel in the 1st. Channel walls are constituted [2nd] by the transparent muscle and it will be in a state with the remaining opaque portion of a mask

(negative-mold mask). Since any undercuts are not expected by this method by the 3rd, the size of a mask must be correctly in agreement with the size of the meant channel and channel walls.

[0199]

Then, a channel is manufactured by carrying out the spin coat of the UV sensitivity polyamide solution on the surface of a substrate to a depth of about 10 micrometers first. It is necessary for polyamide to remain in the field exposed by UV light at a position, therefore to make a photo lithography mask into a negative picture. A mask pattern is stamped on polyamide photoresist by irradiating with UV light. The field of the polyamide layer under the transparent portion of a mask is stabilized by bridge construction by a UV radiation line. The remaining portion of a polyamide layer dissolves with a suitable developer. Bridge construction forms the straight side attachment wall held between development and a hardening stage. Next, postbake of the glass chip is carried out at about 150 **, and a polyamide layer is stiffened. In this way, macro manufacture of a channel is completed.

[0200]

5.5.5. manufacture of an injection port -- when desirable, an injection port can be manufactured in the substrate which is not supporting the electrode pattern. The hole for injection ports can be manufactured by carrying out a drilling process by either of the drill bits with laser or a diamond tip. Preferably, a size decision is made so that a processed hole may enable pouring of the sample by a micro pipette tip, therefore 500 micrometers is suitable size. Since the desirable size of an injection port is 5 to 10 times the desirable interval between channels, for the channel in movement and a detection area by which spacing was carried out densely, its channel patterns which drawing 16 B converges are more preferred than the straight pattern of drawing 16 A.

[0201]

5.5.6. In order to make the separation lane closed in the melting equipment of a substrate, bonding of the substrate accompanied by a channel and the other substrates must be set and carried out. Both sides are purified thoroughly and the next is made first to contact. About the device of Type I, temperature is steadily raised to the annealing temperature of about 500-600 **, is held with this annealing temperature for several hours, and ensures bonding with the good surface. A flat silica plate is made to carry out melting to the polyamide surface of a channel at a lower temperature of about 200 ** about the device of Type II.

[0202]

5.6. The main advantages of the side of an electrode design of explanation this invention of electrode structure are being able to provide a means gathering the charged particle substantially condensed before separation to a limited region. The particle concentration of the remainder of a device falls by this set. This advantage becomes effective again, when a device

is operated according to the following steps. That is, in the first place, a charged particle is uniformly supplied to a device, a device is sealed, the focus of the charged particle is carried out to said limited region, and, finally separation is caused [second / third].

[0203]

A decollator becomes a cell adjoined for [a majority of] holding the charged particle of two or more kinds, and its (to right hand) adjoining cell from the mechanism to which a part for a kind unique ratio (alpha (kind)) is moved among the quantity of several kinds in a cell from each cell. By repeatedly operation, it begins from the initial state which has a complete range in a left-hand cell substantially, movement and separation of a kind take place, and it moves to right-hand side. what is called a Feynman ratchet (R. -- P.Feynman et al., 1996, The Feynman Lectureson Phyiscs, and Vl. 1 --) [Assison-Wesley, Reading and] MA) is such a decollator. The concentration of a certain kind of cell unit decreases substantially during separation of a kind, and it is known that a part for the concentration of origin will be distributed to many cells.

[0204]

The basic principle of operation of the Feynman ratchet is based on the difference in the diffusibility of many charged particles. Electric unsymmetrical potential is formed in a device but spatially periodically. If potential is turned on, particles will be diffused freely. While the particles diffused quickly move to the potential well which adjoins during the next "one", the particles of low diffusibility do not move mostly. Thus, separation takes place. Bier and Astumian (M. Bier and R.D.Astumian, 1966, Bioelectrochem. Bioenerg. 39:67; 1996, Phys.Rev.Lett.76:4277) are mutual -- ******** being carried out and, The electrode connected to the voltage source by the easy method shows the easy example of such a device mostly arranged in the shape of linearity. A required thing is offset or the unsymmetrical chisel of the diffusion process between cells, the move process between cells and a move focus (diffusion center), and a cell border. He could understand the details of the function of the device of this invention by referring to this.

[0205]

This invention provides the improved version of the Feynman ratchet. One advantage of the design currently indicated by this specification is that a re-focus is carried out to a different point for every kind from which the separation kind distributed over many cells differs. For this reason, a thing like the weak signal distributed over many cells is locally brought together in the cell of a small number of the part decided depending on a kind, and these kinds of detectivity is dramatically raised by considering it as a strong signal. Drawing 20 a and drawing 20 b present the device design which attains the schematic depiction and such a re-focus of the re-focus effect in what condensed (and also in case of 22).

[0206]

The usefulness to the size fractionation of this device increases by this re-focus ability. Such a

re-focus, for example before the hybridization in one liquid phase size separation / hybridization chip, For example, probably, it will be [to use a device for the size fractionation of a hybridization probe] suitable to see the hybridization result of only the 100 - 500 base range.

[0207]
Another advantage of this invention is that an electrode design can turn the candidate for detection to Chuo Line of a separation channel continuously (this was known in the advanced technology only within cases other than use of the electric potential for heightening the Feynman rachet effect.). This, The optical version of a device. (A.Ashkin, 1970, Phys.Rev.Lett.24:156; A.Ashkin, 1986, Optics Lett. 11:288; L.P. Faucheux, 1995, Phys.Rev.Lett74:.) Both 1504 and an electric polarization version (D. Long et al., 1996, Phys.Rev.Lett.76:3858; J, Rousselet et al., 1994, Nature 370:446) are indicated.
[0208]
Other advantages of a design of this invention are that the substance in contact with an electrolyte can make the minimum for it to be substantially the same and to obtain through all the separation channels, a charged particle, and inter-electrode contact. The particles (for example, DNA) by which electrification was carried out to some extent tend to receive a chemical interaction with the surface in a separation channel. Therefore, it is strongly desirable to make the interaction of a charged particle-electrode into the minimum. This design attains this.
[0209]
In one example of a design in which the further advantage was shown by this invention, since an electrode does not gear mutually, about the special size of a small electrode, an assembly of a device originates in the short circuit between the electrodes which approached, and is not barred by the low yield.
[0210]
This invention can be used for causing movement of DNA by the Feynman ratchet mechanism. The device of this invention has the use of increasing all the separation and motions using the Feynman ratchet of a form. This device can be used for increasing detectivity. This device can be used for size fractionation and recovery (even if it precedes other analysis technology like DNA hybridization, it is [be / it / under / other analysis technology / also setting] also as a thing of the analysis technology itself [other]). Moreover it may change a design into an above-mentioned optical Feynman ratchet design, it can occur the pattern of the light used as optical tweezers (optical tweezers) using a holograph diffraction grating arbitrarily.
[0211]
The mode of the Feynman ratchet device of this invention shown in drawing 18 is called the "quad symmetry (symmetrical with the four quarters)" device, or the electrode. The electrode

120 which geared mutually [linear shape] is used. They are connected to at least four connection pads. The connection pad is connected to the feed voltage machine which has switch capability through an electric wire (positive, the upper right, and the lower left are negative in the upper right and the lower right), or an electric probe in cross shape.The central focus gap 110 is between connection pads. In order to make a substrate like crystal or silicon oxide paste, an electrode pattern is built with the platinum which has a titanium adhesive layer, and it deals in it. According to electrode width, a desired electrode pattern can be attained by a size width of 1 to 100 microns using the standard art of minute manufacture.

[0212]

The desirable mode of operation of said device is explained by the example of the sake in the case of the DNA analysis object which carried out electrification to negative, without losing generality. A device is cleaned first or the prevention from adhesion to the device of an analysis object is processed (S. it uses into this specification as application and reference on Henck and American patent application serial number 60 / December 3, 1997 [067, 387, and]). A little dilution DNA solutions (it is 2microl at the concentration of for example, 4 pmol/mu l) are added on the surface of a device. Next, a solution layer about 10 microns or less deep is made using coverslip. A seal constituent like ultraviolet-rays therapy adhesives is added at the end of [all the] coverslip. Next, a device is operated by the usual method, it is connected as mentioned above, and almost all DNAs are brought together in a central electrode (with the potential periodic load to a device, bias other than zero may bring about more rapid concentration of DNA to the central focus gap 110 as a result). When changing after all so that a feed voltage machine may supply positive voltage to the bond pad of the upper right and the lower left, separation arises. - It is got blocked and separation is produced according to the usual Feynman ratchet mechanism (it is zero bias to periodic potential). The separated kind is detected by the standard optical technique like a fluorescence microscope.

[0213]

The optical pattern relevant to the electrode design "for quad" can be constituted using other optical components known for high power laser, beam diffusion and a convergent lens, the holography diffraction element, and this aforementioned field. Using such a pattern, in order to attain separation, A. Ashkin, 1970, Phys.Rev.Lett.24:156; It is indicated to A.Ashkin, 1986, Optics Lett.11:288;, and L.P.Faucheeux, 1995, and Phys.Rev.Lett.74:1504.

[0214]

The design of another electrode is illustrated to drawing 19. This design is similar with four symmetrical designs, and has the main focus gap 110, the electrode 120, and the connection pad 130 as above-mentioned. In this case, said electrode includes a right angle along the diagonal line of said device. This right angle fluctuates potential via said device by the method of moving the charged particle which is slightly separated from a diagonal line and has been

arranged so that a charged particle may begin to move in the corner direction by the side of the upper left of said device to a diagonal direction. DNA is condensed along with the center line all the time among a partition process, thereby, I hear that the detection after separation becomes easy, and it has the advantage. The shown design can be manufactured using straight-line mask designing (an angle requires an extensive mask work). By changing an angle in the mask pattern of an electrode, the same effect as what was shown in drawing 22 can be acquired.

[0215]

As mentioned above, it is desirable that it is [after separating a sample] easily detectable, and it is desirable to collect samples after division. The device shown in drawing 20 a makes this detection and recovery easy. All over the separation section 330, as described above, load of the sample is carried out and it dissociates. A sample moves to the re-focus sections 340 and 350 further by using suitable voltage from a voltage supply source, and switching the controller 310 via the electrical conduction line 320 at another connection pad 130 (it is at a minimum of 5 on each side of said device). For example, when two sorts of things exist in a sample, using a suitable design parameter, those kinds are separated substantially, and when each is found out by one side of said two re-focus sections, a culmination is reached. next, said controller is changed and it is made for said re-focus section itself of each to function as four symmetrical devices Thereby, the separated sample is accumulated into the separate section in the main focus gap 110 which exists in each re-focus section 340 and 350. The principle of operation is shown in drawing 20 b. as having described above -- load and seal -- and when a focus is carried out, two kinds of each accumulation are seen on the left-hand side of said device, and the concentration is shown by the curve 380. After dissociating, as shown by the curves 384 and 388, the first concentrate is distributed to many cells of said device by low concentration per each cell. Each kind remains in the related re-focus section 340 and 350 substantially. After changing a voltage controller, a separate field is made to carry out the re-focus of the various kinds at high concentration, as shown by the curves 392 and 396. These fractions that were separated from the original sample and condensed can be detected easily, or can be taken out from said device for the further use and analysis.

[0216]

In engineering drawing of the device indicated in detail, the substantial contact an electrode and for detection exists upwards. It is thought that it is important when this contact uses this device well. However, it is preferred to control a surface interaction with the separation channel for detection. In consideration of these things, a design becomes what was shown in drawing 21 which suppressed contact an electrode and for detection to the minimum. the basic base 410 made with a suitable material is chosen, and it processes so that it may have processing or the surface characteristic for which micro processing was carried out and it was suitable to

the candidate for detection (quartz -- a DNA analysis sake -- RCA -- it is clean and processes.) S. Please refer to Henck, U. S. Patent Application Ser. No. 60/067, 387, and December 3, 1997 application. This application shall include the whole sentence in this specification by reference. Si wafers 420 and 430 and Pt electrode which have oxide coating or other coating are processed as mentioned above. This wafer is combined with a proper place as shown in a perspective diagram. It processes and washes [process and], and the covering 440 made with a suitable material at the end is attached, and seals this device so that a separation channel may be included. The width of the channel 450 is more slightly [than the exposed basic base] large, and it is made for a channel to lap with the edge of the wafer 470. The small electrode-sample contact area 460 is made as a result. This is clear from the plan shown in drawing 21, and a detail view. Wearing and an operation of a device are the same as that of ****. In this design, it must be careful of an electrode not to carry out mutual fitting so that production of a device may not be barred by the fall of the yield by an adjoining inter-electrode short circuit for the small size of a characteristic electrode.

[0217]

Combining the advantage indicated about above-mentioned drawing 18 - 20, the desirable embodiment of an electrode design is shown in drawing 22, and the details are explained below.

[0218]

The example of a desirable embodiment is shown in drawing 22 as a plan. A short electrode segment adjoins the separation section 330, the focal section 500 is formed together with the focal gap 110, and a sample is first condensed following loading and seal of this device. The potential which a sample experiences via an electric lead is changed using supply of voltage, and switching of the control unit 310. This is carried out by a method which is divided into the composition kind, when a sample crosses the separation section 330. A sample leaves the end (it was shown like right-hand side) of a separation section, and moves to up to some re-focus sections (five are shown in a figure) 520. Ideally, the number of re-focus sections is equivalent to the number of different kinds substantially expected to be contained in the sample of a basis, or the number of the size ranges where judgment is desired. This is made to about 100 using the art of microelement manufacture.

[0219]

According to the details of the electrode structure of the central focus gap 110 neighborhood, some embodiments are possible for 4 symmetrical electrode designs. Typically, as shown, for example in drawing 18, the cross wirings (the upper left and the lower right are anodes) of the connection pad 130 are carried out. In this figure, a central electrode gap shows an earth electrode to the upper part, and shows an anode to the lower part. In a substitute embodiment, a single electrode is removed from the lower part in the upper half of this device, a single

electrode is removed from the upper part in the lower half of this device, or both are removed. This by affecting whether a central electrode gap is combined with the electrode pair or simple electrode approached and arranged, Or while the candidate for detection is carrying out the focus towards the gap 110, the character of a device is changed by changing the electric charge which will be seen on an electrode central [most]. In the case of for [which carried out electrification to negative] detection (DNA), in a desirable embodiment, the upper electrode from the lower half of this device is removed. While the candidate for detection carries out a focus towards the gap 110, the center of a device will contain the electrode which was surrounded by two single (it is not a pair) electrodes which carried out electrification to negative and which just carried out electrification. This is preferred in order to attain the best focus to the central gap 110 for [which carried out electrification to negative] detection.
[0220]

[Translation done.]

* NOTICES *

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EXAMPLE

[Example]
6. Calculate the action of a decollator using the desirable model of this invention described by the separation of Section 5.3 of the example 6.1. single stranded DNA. :L which assumes the following device design parameters = 10 micrometers, R= 1 micrometer, 1 cm in length, the potential difference 1V, and an aquosity separation medium. In order to provide 2 base resolution when separating the 100 base ssDNA, t_{on}=1msec and t_{off}=60msec are calculated as optimal thing. Sum total separation time is 60 minutes. These designs and operation parameters are used, About the mixture of the ssDNA fragment of the length 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100, (It is known as an available ladder for standard 10 base sequence determination from Research Genetics, Hunstville, and aluminum), The action of a device is calculated.
[0221]
Drawing 17 has illustrated the action a device is predicted to be. A horizontal axis records the increasing sum total separation time, and the vertical axis is recording the concentration of DNA which leaves a device. This graph has illustrated the concentration DNA which leaves a device was predicted to be as a function of separation time. All the DNA fragments of your having to be disengageable are clearly clear.
[0222]
7. The range should not be restricted by the specific embodiment which described a specific embodiment and quotation this invention of the reference on these specifications. In addition to what is explained in this specification, in a person skilled in the art, various corrections of this invention will actually become clear from the above explanation and an accompanying drawing. It has intention of such correction with what enters within the limits of an attached claim.
[0223]

Various publications are quoted by this specification and, as for the indication, entailment of the whole is carried out as reference.

[0224]

8. Computer program for choosing the optimal parameter

```
/*
        calculate parameters for the dna separation device
        Copyright 1996 Curagen Corporation
*/

#include      <math.h>
#include      <stdio.h>
#include      <string.h>
#include      <stdlib.h>

#defineABS(x) ((x)>O?(x):(-(x)))

#definePI 3.141592653589793 /* why not? */
#defineEBREAK 1.e4 /* breakdown field for water */

#defineMINLOG -6.
#defineMAXLOG 1.

/* erfc by polynomial approximation */
#defineA1     0.2548296
#defineA2     -0.28449674
#defineA3     1.4214137
#defineA4     -1.453152
#defineA5     1.0614054
#defineQP     0.3275911
#define
 ERFC(x)( ((((A5*(1./(1.+QP*x))+A4)*(1./(1.+QP*x))+A3)*\

(1./(1.+QP*x))+A2)*(1./(1.+QP*x))+A1)*(1./(1.+Qp*x))*exp(-x*x))

double R,L; /* R is the small spacing, L is the well spacing*/

double alphafn(double d, double t)
{
double alpha,x;
x = R sqrt(4. * d * t);
alpha 0.5 * ERFC(x);
return(alpha);
}

main()
{
double n,dn; /* n and delta n */
int nstrand; /* 1 for ssDNA, 2 for dsDNA */
```

```
double d,d1; /* diffusivity for length n and (n + dn) */
double logt,t,alpha,alphal,dadn,dndasq,cycles,time;
double tbest, timebest,t_on,vO;
int ntmp;
double dtmp;

char line[100];

char *datafile = "data";
FILE *fp;

R = 1.;
L = 10.;

printf("Enter R (smaller spacing) and L (larger spacing) in microns: ");
fgets(line,sizeof(line),stdin);
sscanf(line,"%1f %1f",&R,&L);

R *=  1.e-4; /* convert to cm*/
L *= 1.e-4;
printf ("Device size: R = %lf microns, L = %lf microns\n",
R*1.e4,L*1.e4);

/*
      the breakdown field of water is 1e4 V/cm
      choose VO so 2VO/r = 1e4 V/cm
      */
vO + R * EBREAK / 2.;
/*
      use a maximum overpotential of 2VO = 1 V to avoid electrolysis
      8/
if (vO > 0.5) { vO = 0.5;

printf("V_O = %1f V, generating maximum field of %lf V/cm\n",
vO,2.*vO/R);

printf("N = the length of the sequence\n"
"Delta N = the resolution (1 for sequencing)\n")

while (1) {

printf("Enter N and Delta N: ");
fgets(line,sizeof(line),stdin);
sscanf(line,"%lf %lf",&n,&dn);
if (n < 1) { break;}
printf("Enter 1 for ssDNA or 2 for dsDNA: "); fgets(line,sizeof(line),stdin);
sscanf (line, "%d",&nstrand);
if ((nstrand!=l)&&(nstrand!=2)) { break; }
fp = fopen(datafile,"W") ;

/*      determine the diffusion constants for n and n+l units are cm-2/sec
t-on is the relaxation time for a 200 V potential
*/
if (nstrand == 1) {
t_on    (L-R)*(L-R)*2.24e-4/(R*pow((double) n,0.41));
```

```
t_on *= l.e4; /* convert from cm to microns */
}
else {
t_on    (L-R)*(L-R)*1.12e-4/R;
t_on    1.e4; /* convert from cm to microns */
}
printf("t-on + %1f s\n",t_on);
if (nstrand == 1) {
d = 1.14e-6 * pow(n, -0.59);
d1 = 1.14e-6 * pow(n+dn, -0.59);
}
else {
d = 1.14e-6 / n;
d1 = 1.14e-6 (n+dn);
}

tbest = O.; timebest = 1.e1OO;
for (logt = MINLOG; logt <= MAXLOG; logt += 0.001) {
t = pow(10.,logt);
alpha = alphafn(d,t);
alpha1 = alphafn(dl,t);
dadn = alpha1 - alpha;
if (ABS(dadn) < l.e-6) {continue;}
dndasq = 1. / (dadn * dadn);
cycles = alpha * (1. - alpha) * dndasq;
time = cycles * (t + t_on);
fprintf(fp,"%lf %lf %lf %lf %lf %15.101f\n",
t,time/60.,cycles,alpha,dndasq,dadn);
if (time < timebest) { tbest = t; timebest = time;}
if (time > 10.*timebest) {brcak;}
}
fclose(fp);

t = tbest;
alpha = alphafn(d,t);
alpha1 = alphafn(d1,t);
dadn = alpha1 - alpha;
dndasq = 1. / (dadn * dadn);
cycles = alpha * (1. alpha) dndasq;
time = cycles * (t+t_on);
printf(" N %d Delta %d nstrand %d R (um) %lf L (um) %lf\n",
(int)n,(int)dn,nstrand,1.e4*R,l.e4*L);
printf(" t_on %g vO %g\n",t_on,vO);
printf("\nN = %d +/- %d\n"
"time (min) %lf\n"
"length (cm) %lf\n"
"t_off(sec) %lf\n"
"N_cyc %f \n"
"alpha  %lf\n\n",
(int)n,(int)dn,
time/60.,alpha*cycles*L,t,cycles,alpha);

printf("%lf %lf\n",l.e4*L,alpha*cycles*L);
printf("%lf %lf\n",t+t-on,time/60.);
for (ntmp = 10; ntmp <= 100; ntmp += 10) {
```

```
 dtmp = 1.14e-6 * pow(ntmp, -0.59);
 printf("%d %lf\n",ntmp,alphafn(dtmp,t));
}

printf("End of program.\n");

}
```

[Brief Description of the Drawings]

[Drawing 1]The eliminator implement by this invention is shown.

[Drawing 2]One exploded view of the example of the I-beam of the eliminator implement of drawing 1 is shown.

[Drawing 3]The sectional view which intersects perpendicularly to the separating direction of the instrument of drawing 2 is shown.

[Drawing 4]Drawing 4 A and 4B show the details of the electrode of the instrument of drawing 2, and the potential generated by this electrode.

[Drawing 5]The sectional view along the separating direction of the instrument of drawing 2 is shown.

[Drawing 6]The loading part of the instrument of drawing 2 is shown.

[Drawing 7]One exploded view of the II type example of the eliminator implement of drawing 1 is shown.

[Drawing 8]The sectional view which intersects perpendicularly to the separating direction of the instrument of drawing 7 is shown.

[Drawing 9]Drawing 9 A thru/or 9E summarize and show operation of the method of this invention.

[Drawing 10]The gestalt of the potential which may suit using it in the method of drawing 9 A thru/or 9E is shown.

[Drawing 11]Drawing 11 A thru/or 11D show the details of the action of the particle concentration profile in two adjoining potential wells in the method of drawing 9 A thru/or 9E.

[Drawing 12]Drawing 12 A thru/or 12E show the action of the detailed particle concentration profile in two or more adjoining potential wells in the method of drawing 9 A thru/or 9E.

[Drawing 13]The action of t_{off} opposite T_{tot} about the desirable method for choosing the operation parameter of the method of drawing 9 A thru/or 9E is shown.

[Drawing 14]The action of percentage pair T_{tot} of break-up of a DNA molecule when the parameter which operates a method in accordance with the desirable method for choosing the operation parameter of the method of drawing 9 A thru/or 9E is chosen is shown.

[Drawing 15]The typical photograph monotonous mask for manufacturing the electrode for the instrument of drawing 2 is shown.

[Drawing 16]drawing 16 A thru/or 16B show the typical photograph monotonous mask for manufacturing the channel for the instruments of drawing 2 -- and [Drawing 17]The example of separation on imagination of the DNA molecule according to the method of drawing 9 A thru/or 9E is shown.

[Drawing 18]The arrangement of the electrode clenched by a central focus gap and quad symmetry is shown.

[Drawing 19]An analysis object shows the quad symmetrical design continuously sent into the diagonal center line of a device.

[Drawing 20]Drawing 20 A shows the design concept of a separation electrode section of using for the re-focus of an after-separation sample.

Drawing 20 B shows the advantage of detection by the electrode design shown in drawing 20 A.

[Drawing 21]All separation channel walls consist of same material, and contact symmetrical with an electrode and detection shows the embodiment of the device of this invention which is the minimum.

[Drawing 22]The desirable embodiment of the device of this invention included the advantage shown in drawing 18 thru/or drawing 20 is shown.

[Translation done.]

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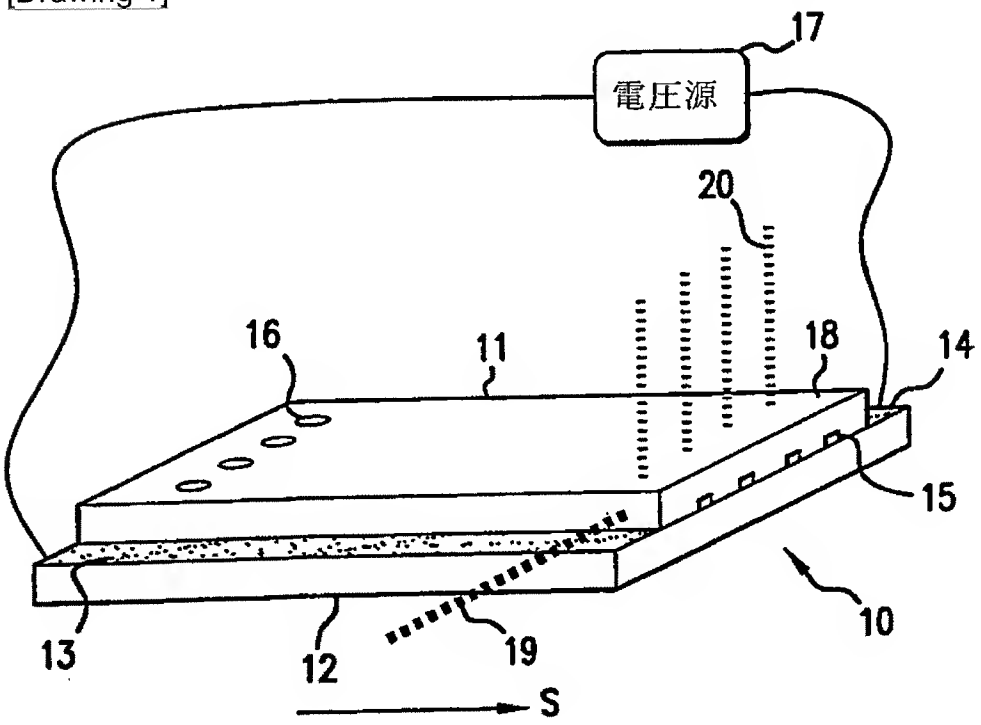
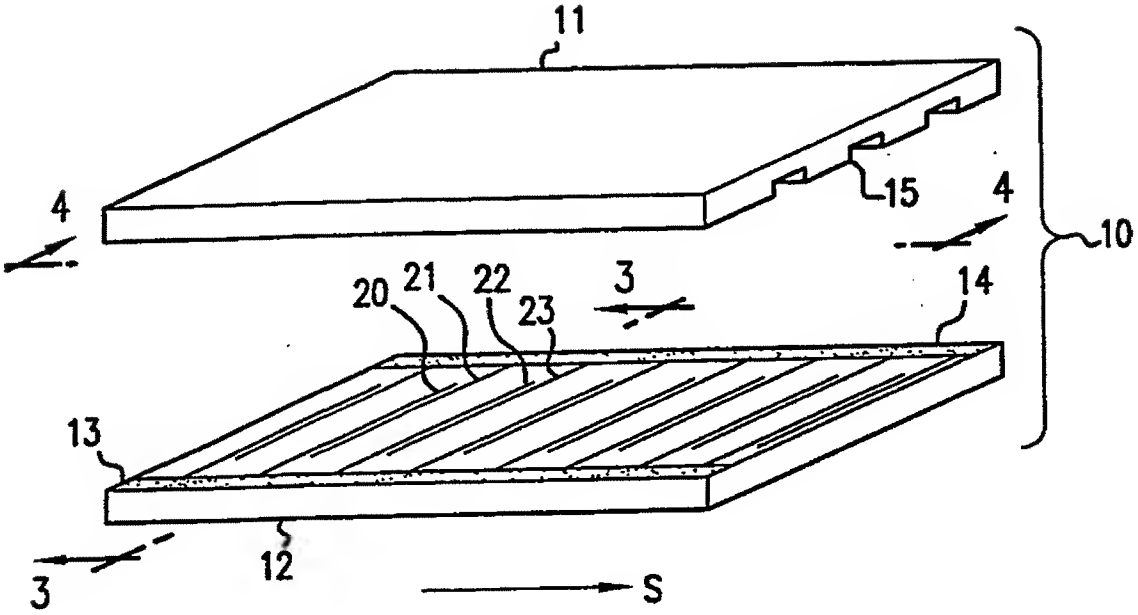
DRAWINGS

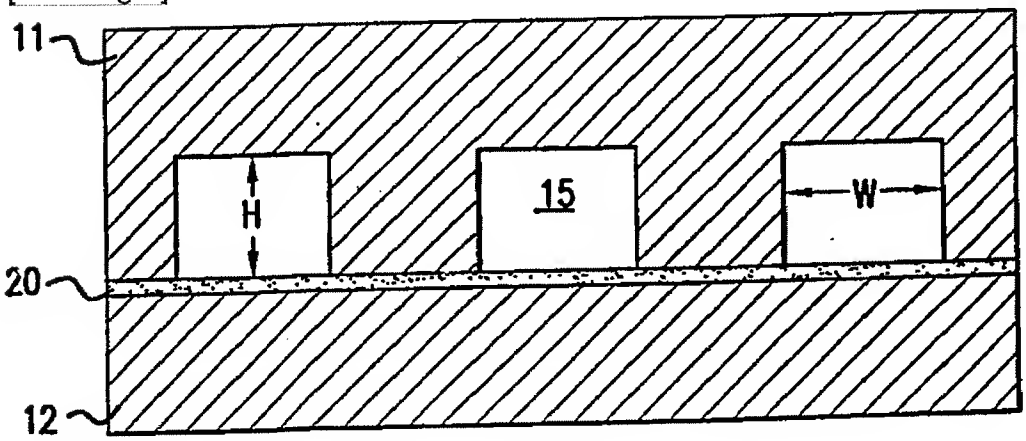
[Drawing 1]



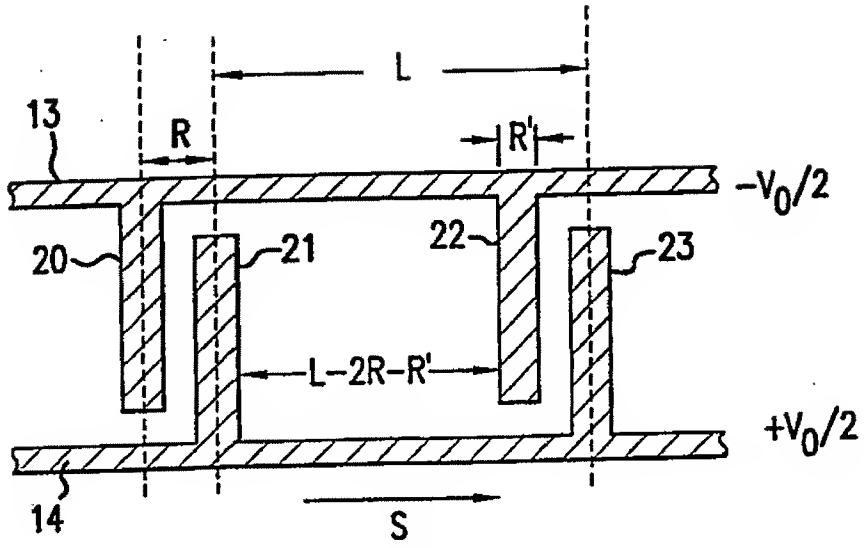
[Drawing 2]



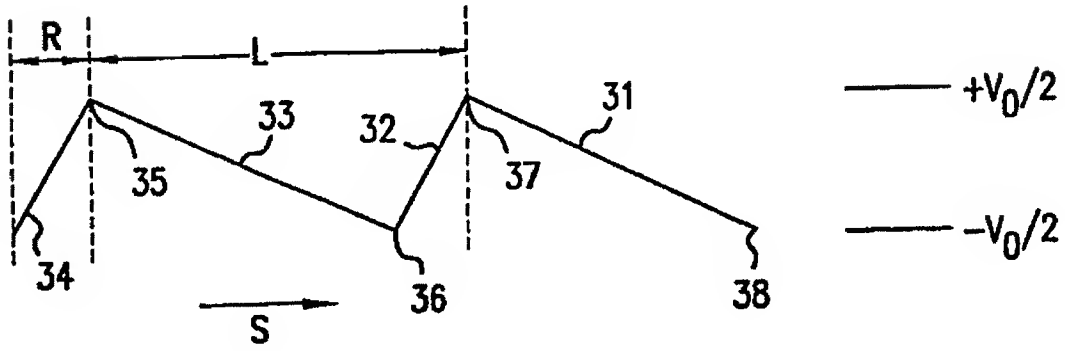
[Drawing 3]



[Drawing 4]

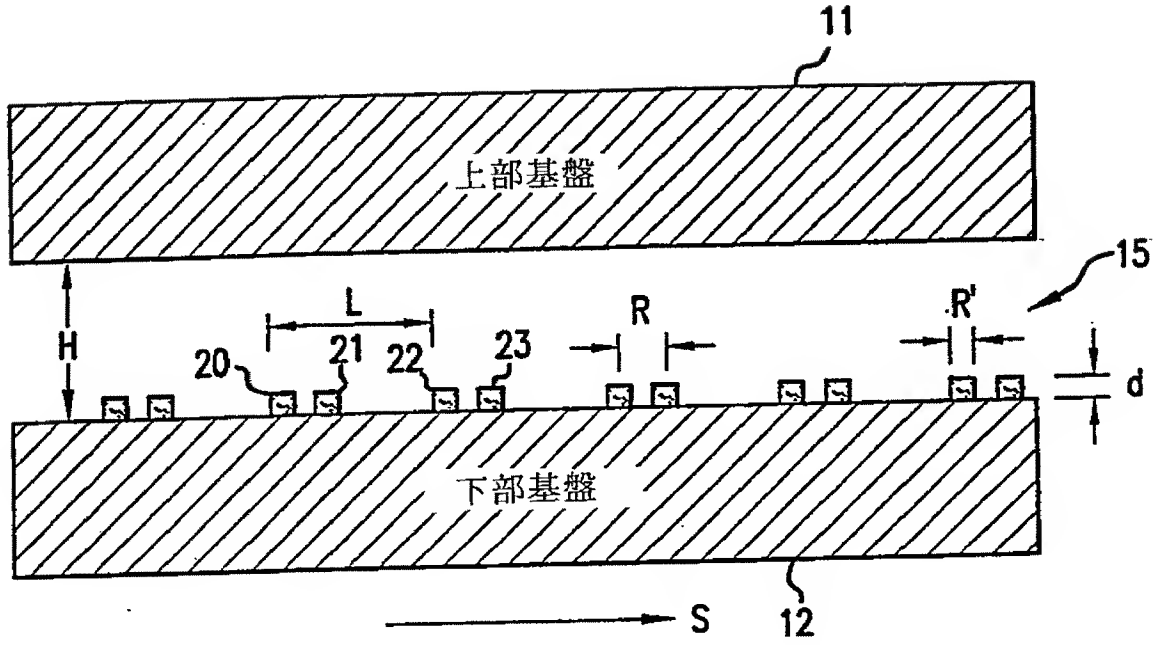


4A

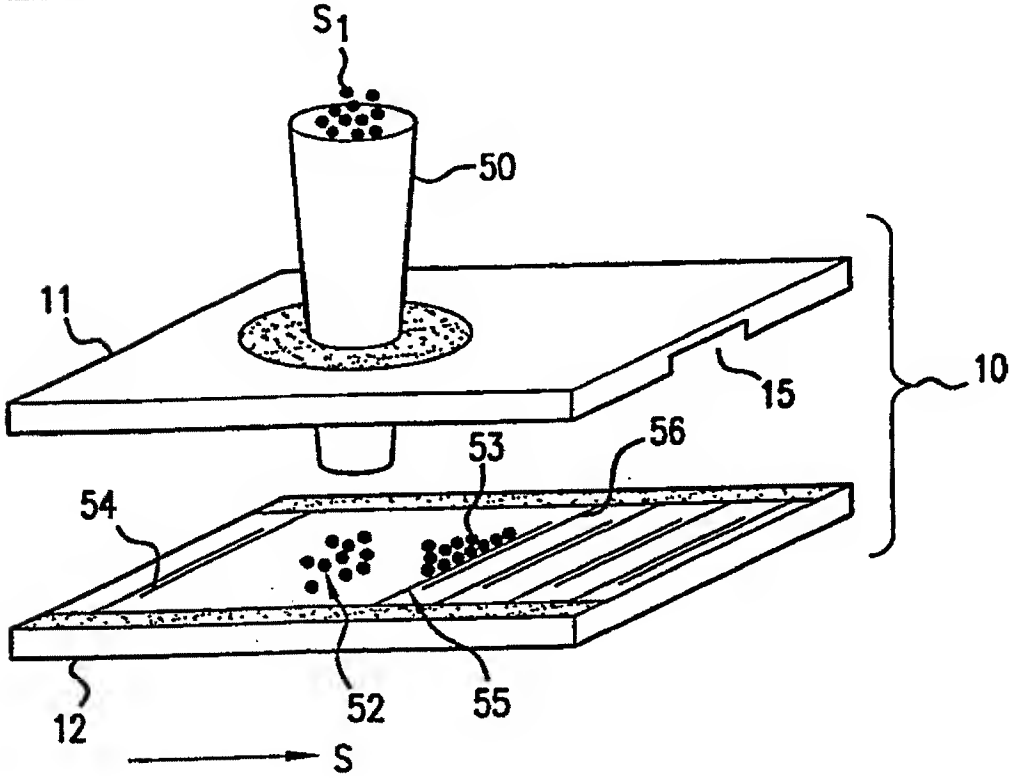


4B

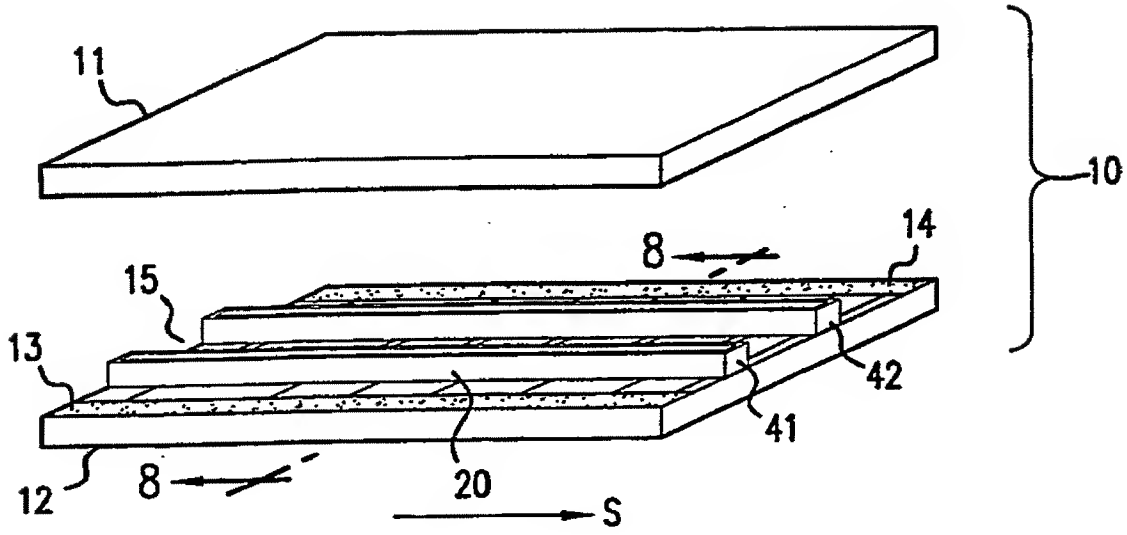
[Drawing 5]



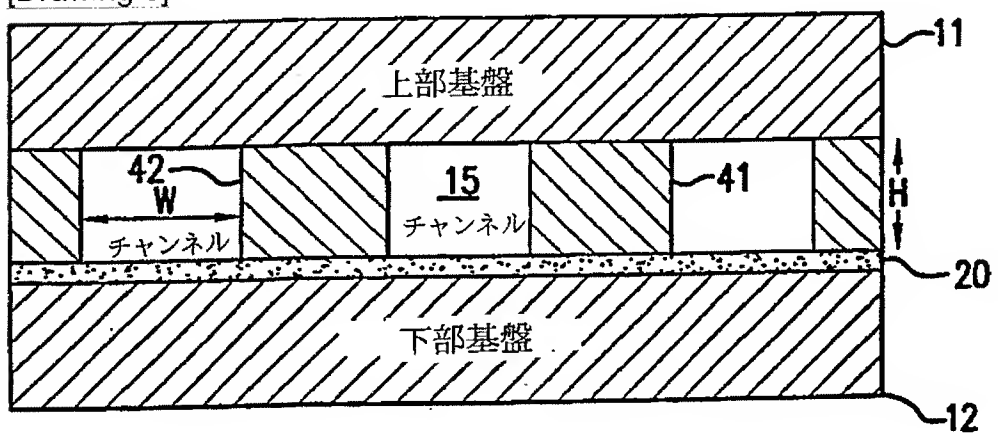
[Drawing 6]



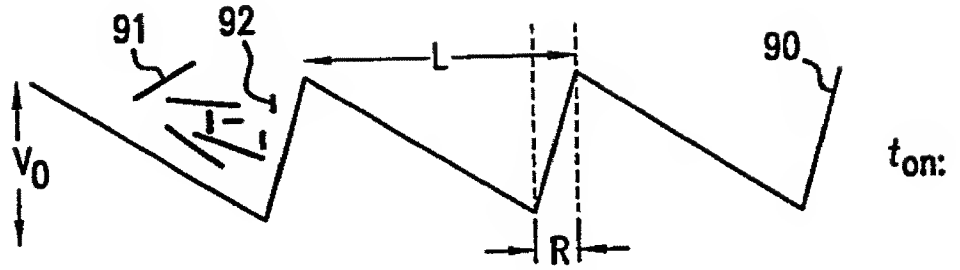
[Drawing 7]



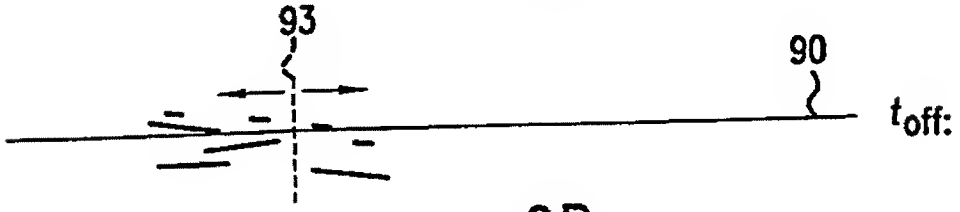
[Drawing 8]



[Drawing 9]

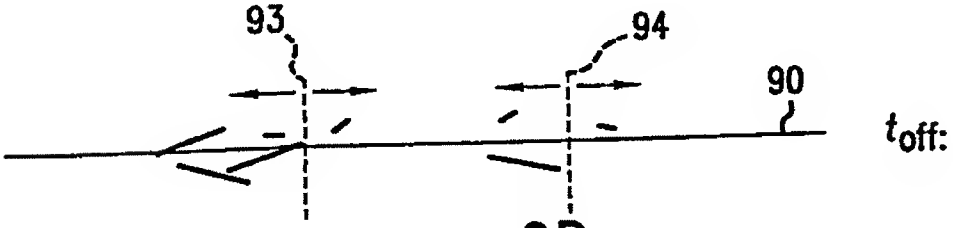


9A

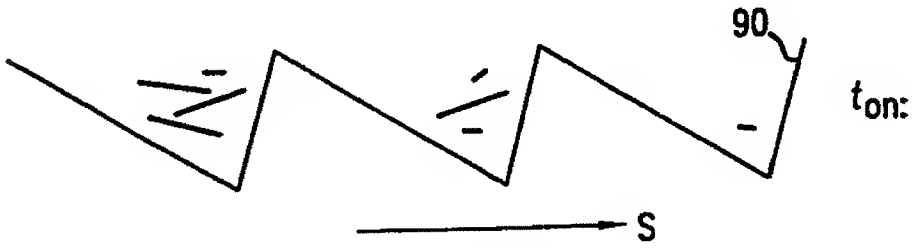


9B

9C

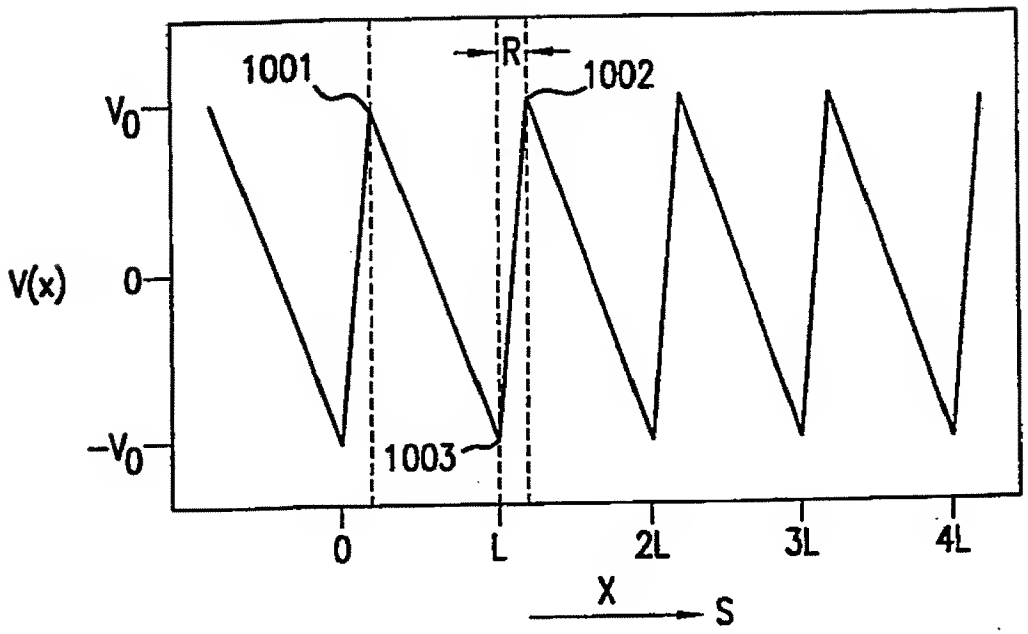


9D

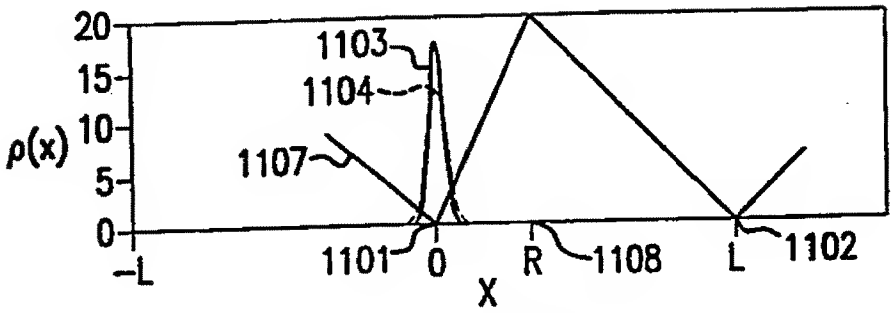


9E

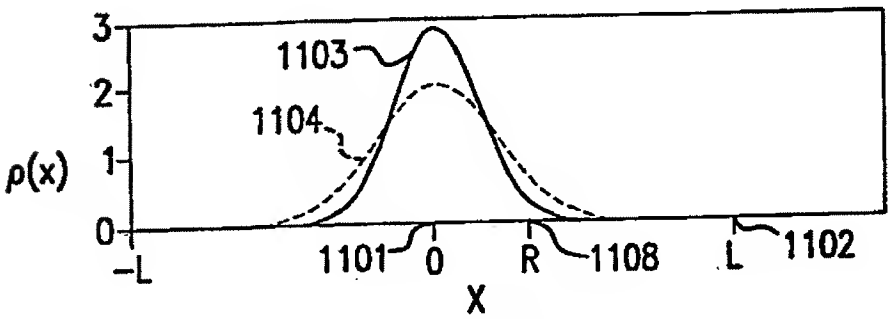
[Drawing 10]



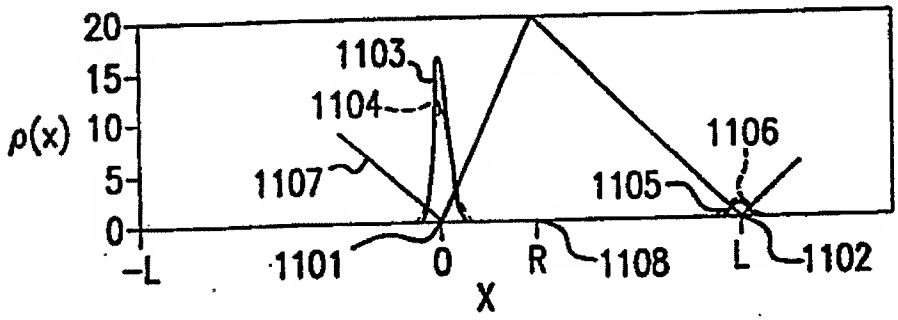
[Drawing 11]



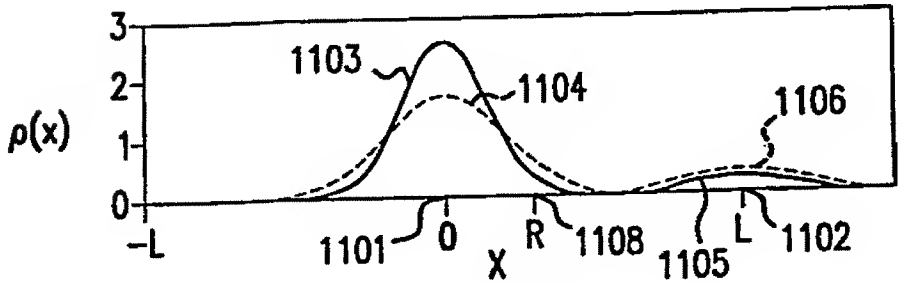
11A



11B

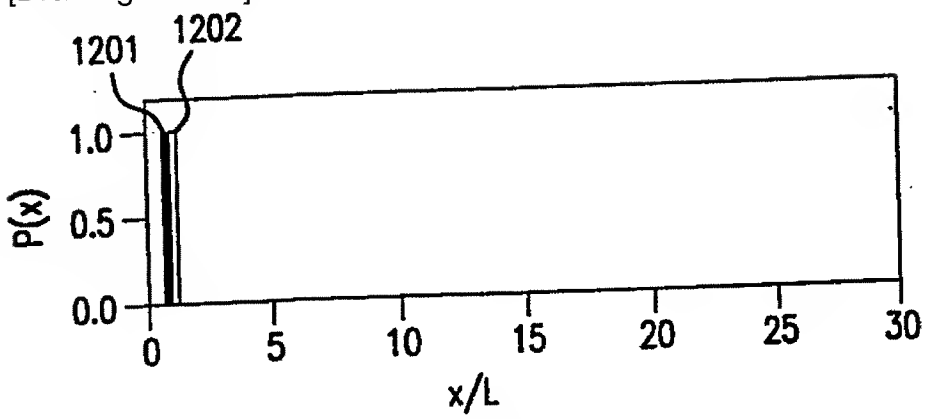


11C

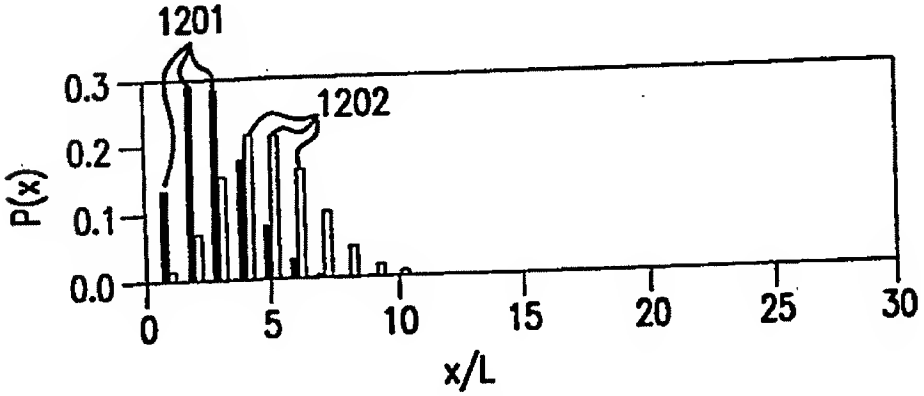


11D

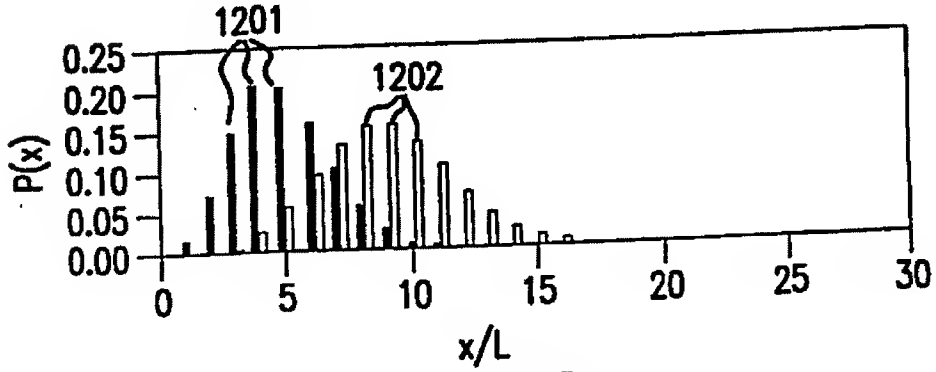
[Drawing 12 A-C]



12A

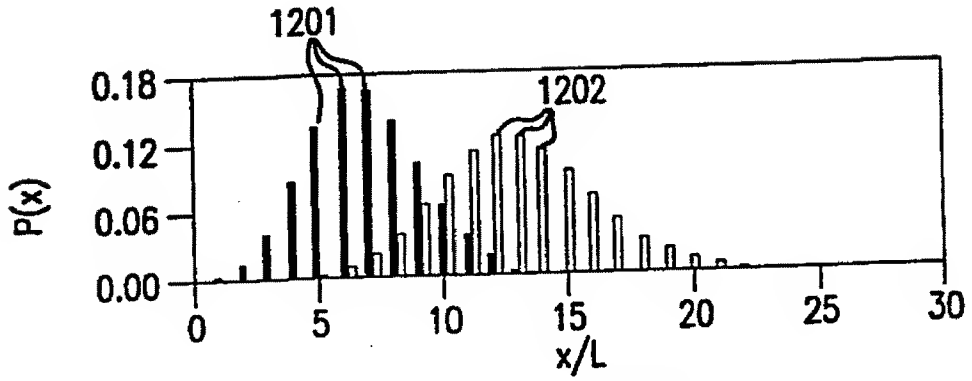


12B

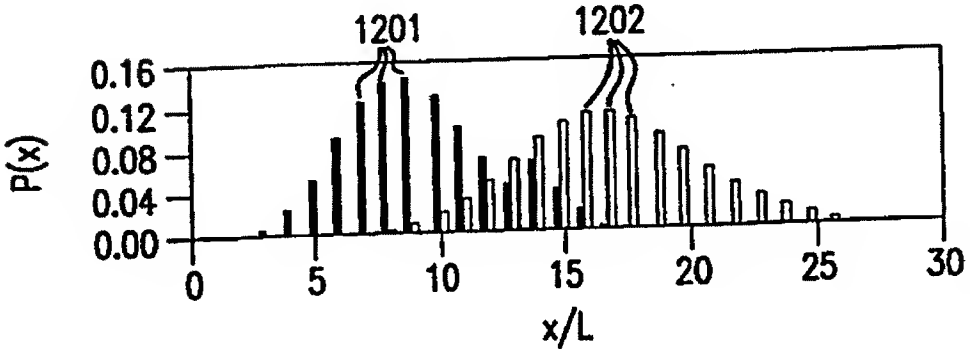


12C

[Drawing 12 D-E]

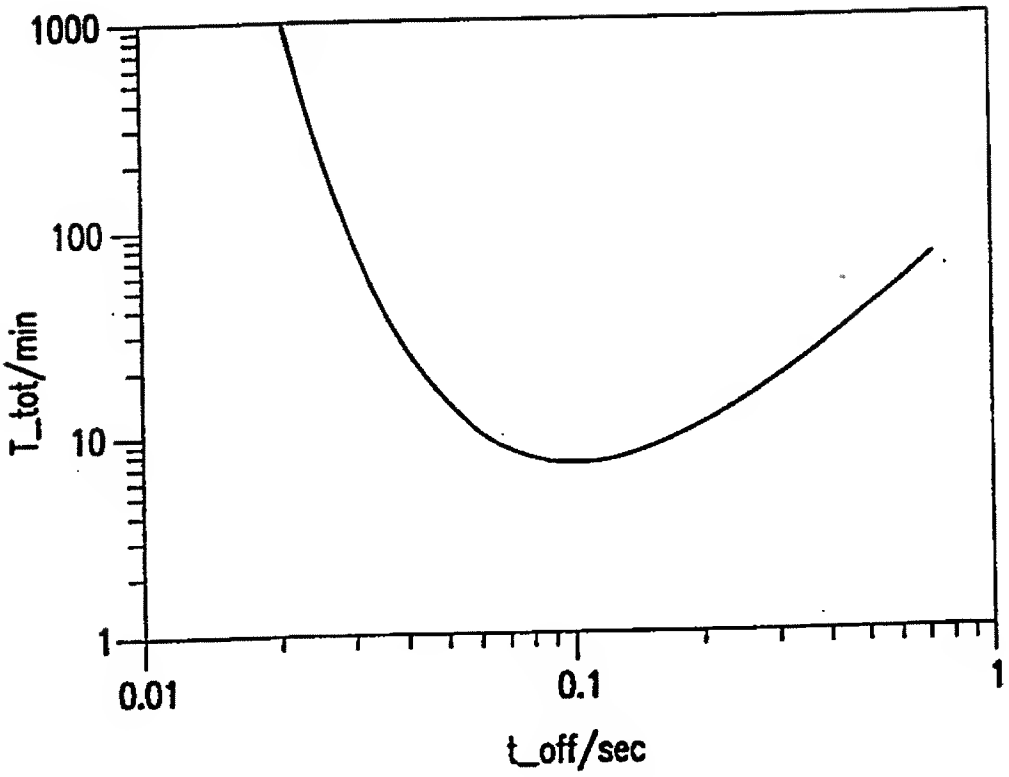


12D

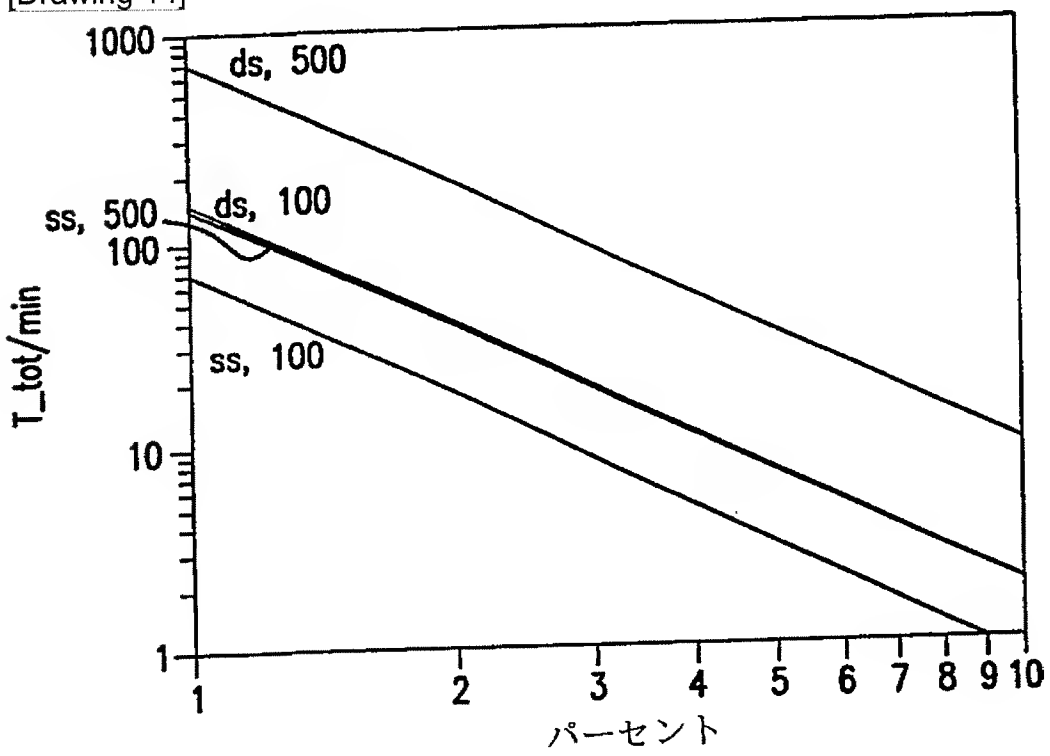


12E

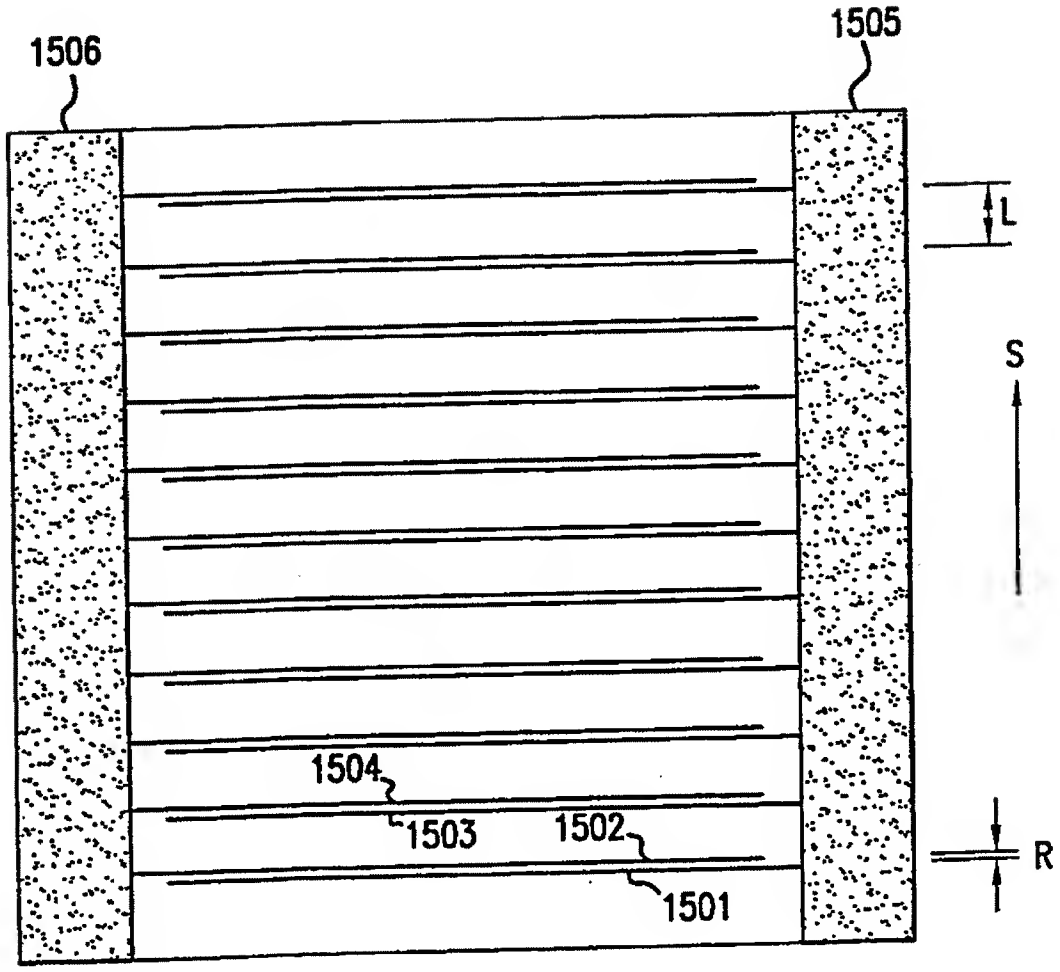
[Drawing 13]



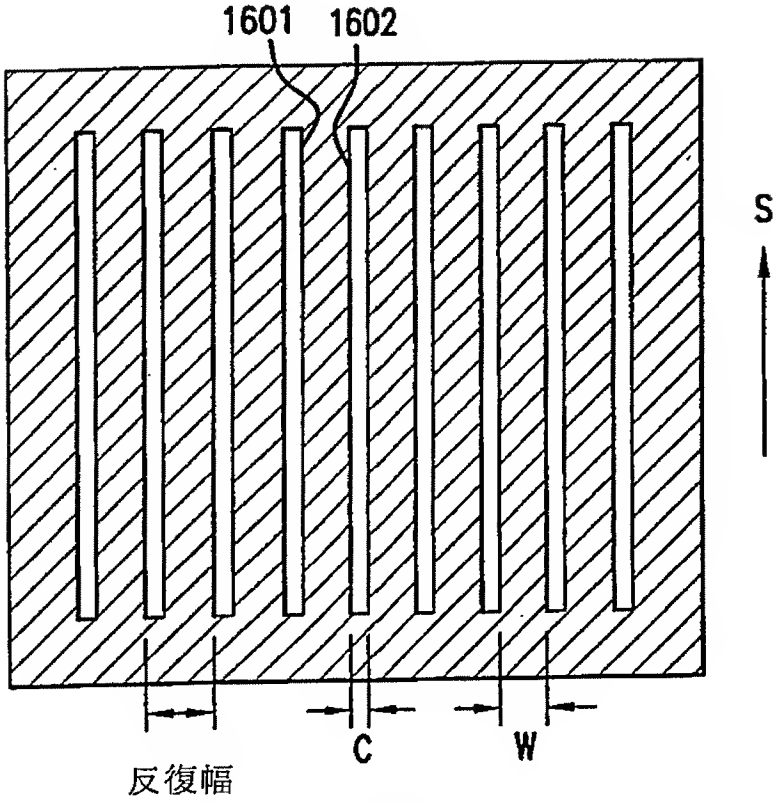
[Drawing 14]



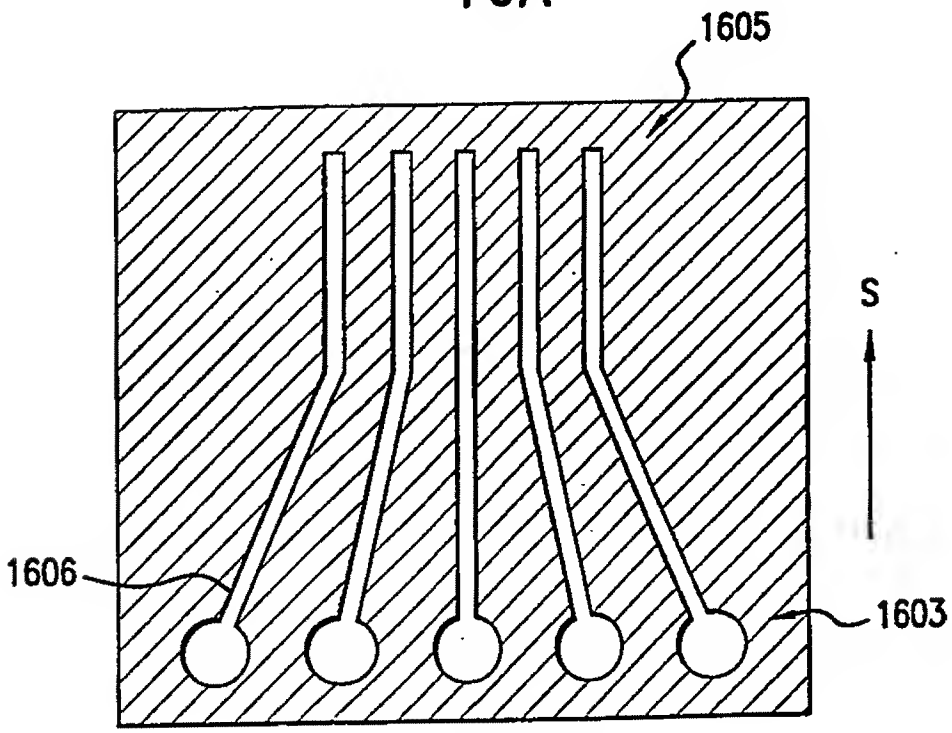
[Drawing 15]



[Drawing 16]

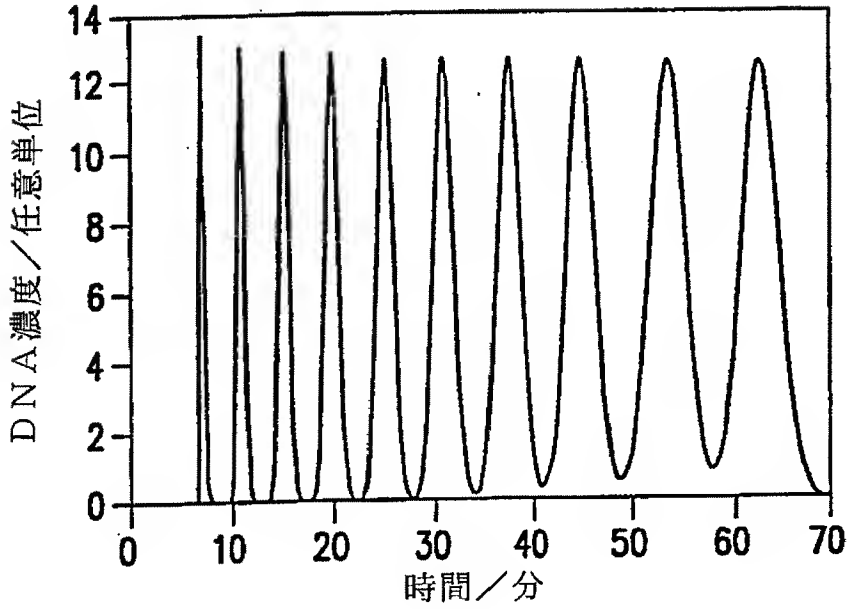


16A

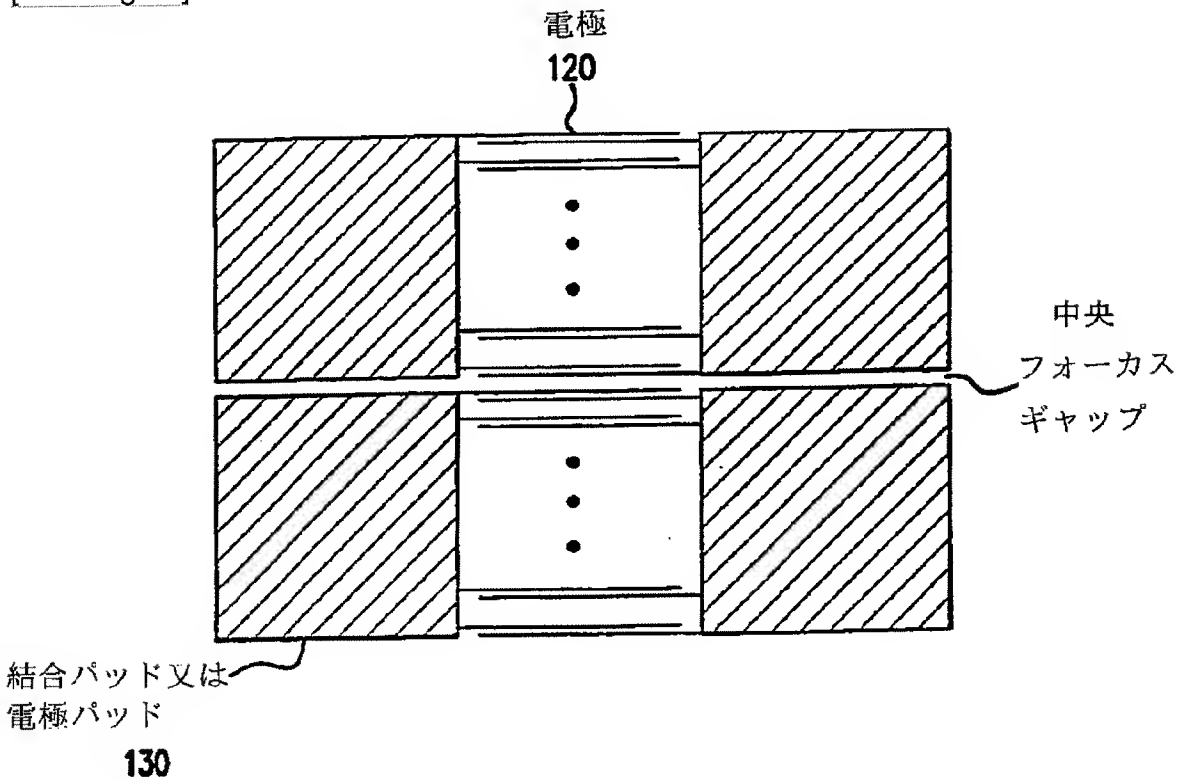


16B

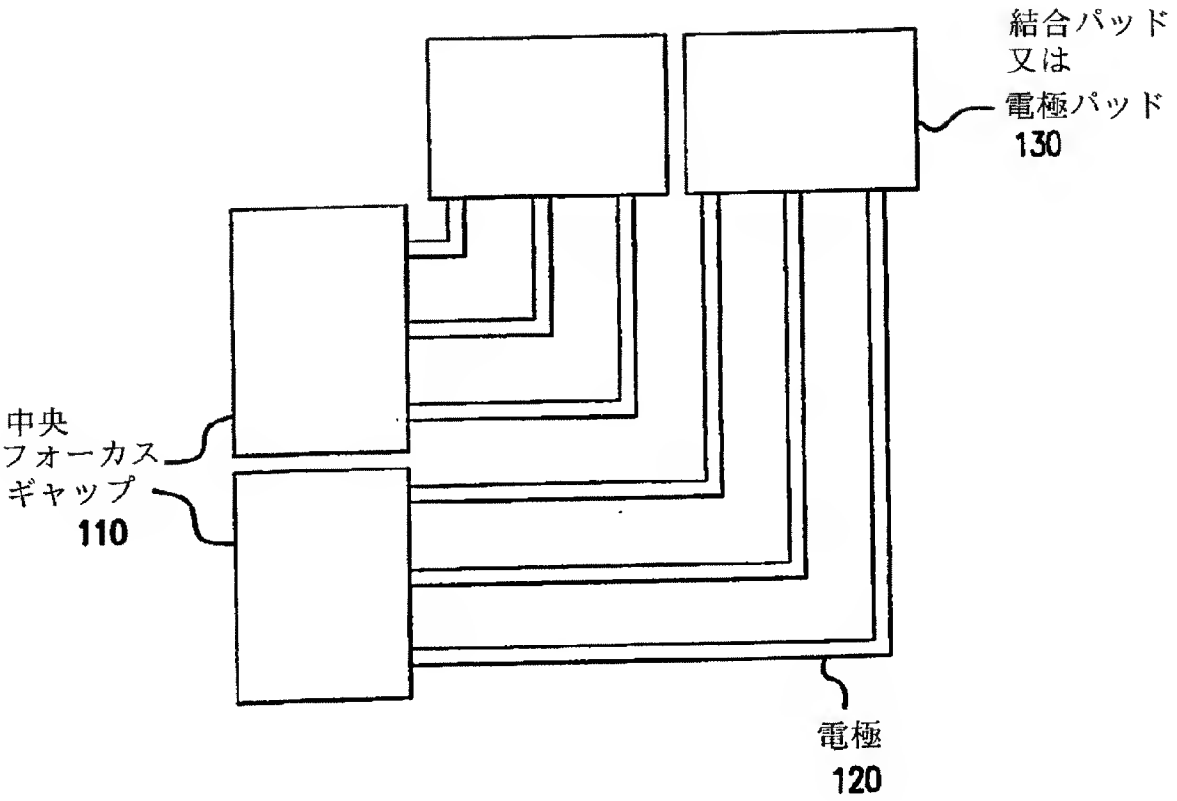
[Drawing 17]



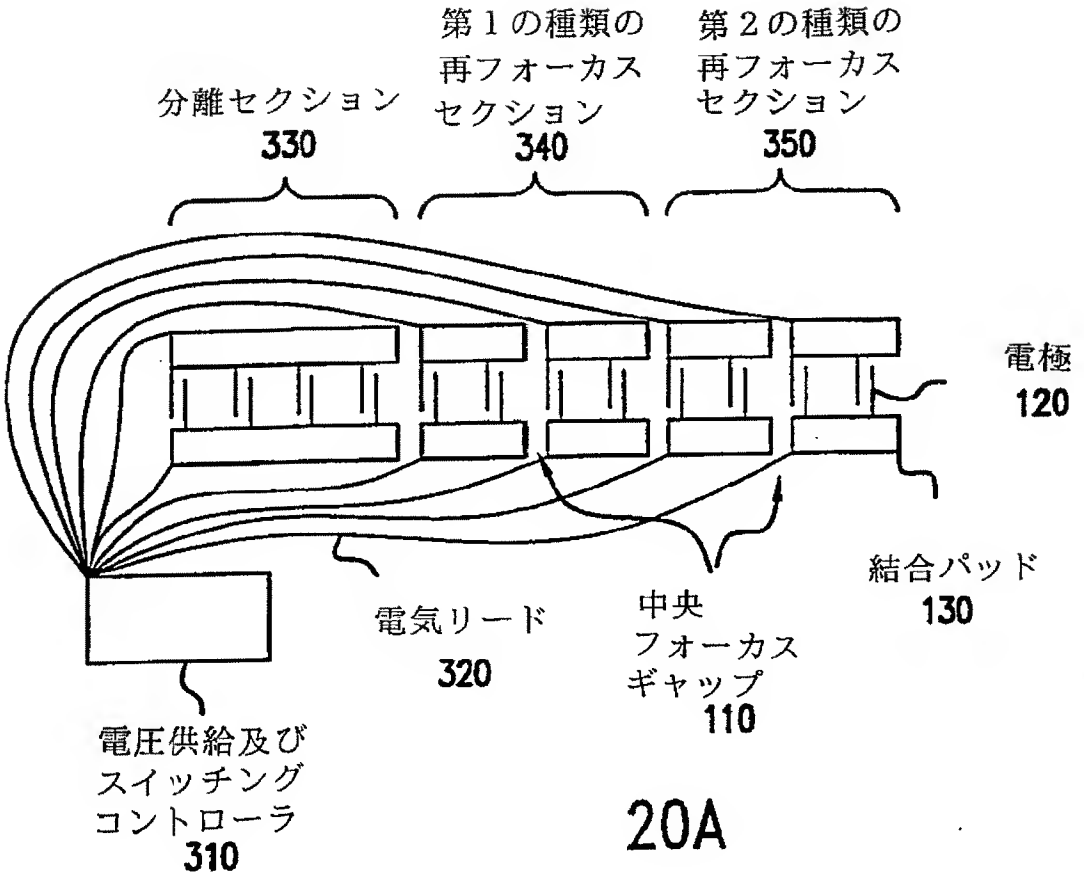
[Drawing 18]



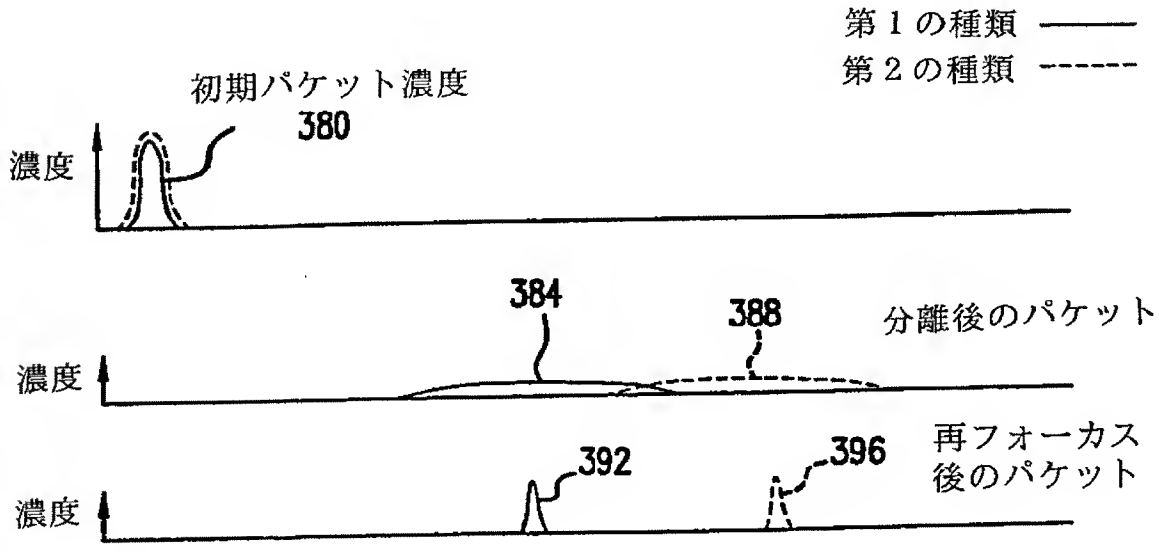
[Drawing 19]



[Drawing 20]

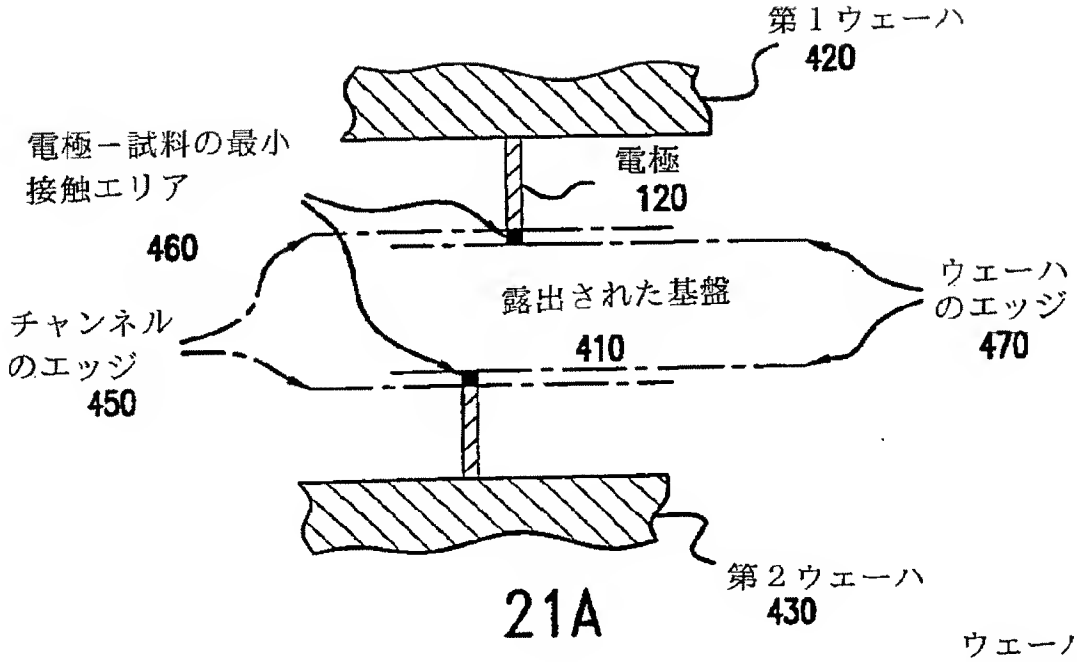


20A

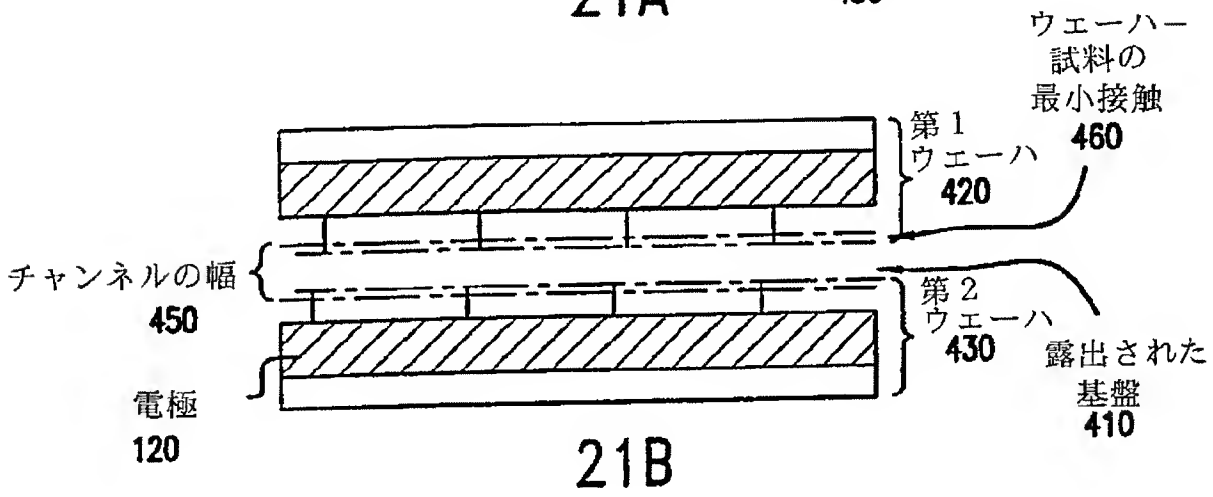


20B

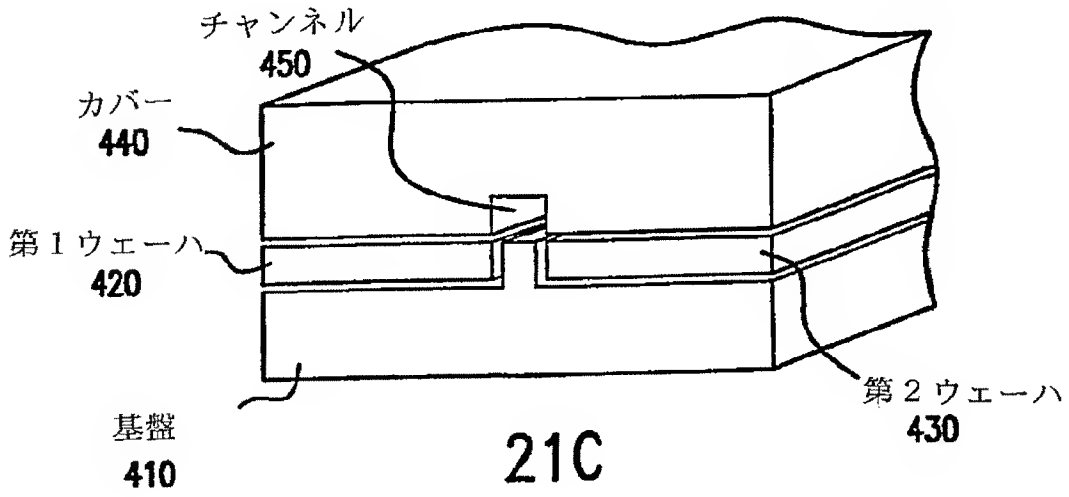
[Drawing 21]



21A

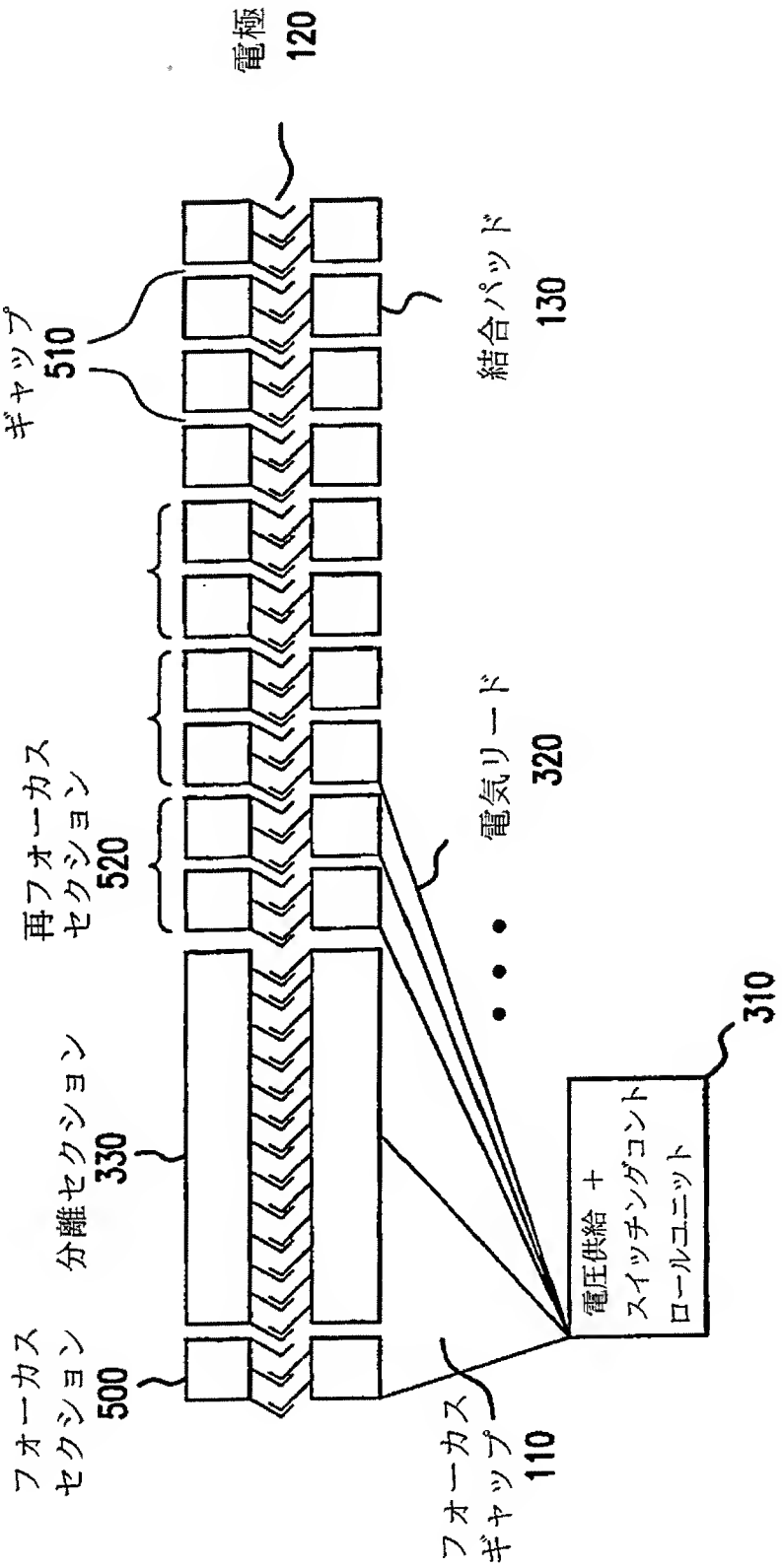


21B



21C

[Drawing 22]



[Translation done.]